```
=> d his

     (FILE 'HOME' ENTERED AT 12:06:58 ON 10 MAY 2004)

     FILE 'REGISTRY' ENTERED AT 12:07:06 ON 10 MAY 2004
                E POLYETHYLENE GLYCOL/CN
L1              1 S E3
                E INTERFERON/CN
                E INTERFERON A/CN
                E INTERFERON A 2B/CN
                E INTERFERON A -2B/CN
                E INTERFERON A-2B/CN
L2              2 S E3-4
L3              1 S 215647-85-1

     FILE 'CAPLUS' ENTERED AT 12:09:32 ON 10 MAY 2004
L4             38 S L3
L5          99849 S L1 OR PEG OR PEGYLAT? OR POLYETHYLENE GLYCOL
L6          64905 S L3 OR INTERFERON?
L7          98485 S CONJUGAT?
L8            105 S L5 (L) L6 (L)  L7
                  SET SFIELD BI
L9          24364 S DI PEPTIDE? OR DIPEPTIDE? OR MET(2W) NLE OR MET (2W) ALA OR G
L10          2400 S METHIONINE (2W) NORLEUCINE OR METHIONINE (2W) ALANINE OR GLUT
L11             1 S L8 AND (L9 OR L10)
L12             3 S L5 (L) L7 (L) (L9 OR L10)
L13            18 S L5 (L) (L9 OR L10)
L14             6 S L13 AND DERIV?
L15             8 S L11 OR L12 OR L14
L16            41 S POLYMER?  (L) L6 (L) L7
L17             1 S L16 AND (L9 OR L10)
L18         94436 S POLYOXYALKYLENE? OR POLYVINYLP?
L19            84 S L18 (L) L6 (L) L7
L20             0 S L19 AND (L9 OR L10)
L21             9 S LINK? AND L19
L22             2 S L19 AND L3
                  SET SFIELD OBI
L23            41 S L19 (L) INTERFERON? (L) ALPHA##
L24            23 S L23 AND 2A
                  SET SFIELD BI
L25         37525 S REPORTER?
L26             0 S L25 AND L24
L27             9 S L5 AND L6 AND (L9 OR L10)
L28            16 S L15 OR L27
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=> fil reg
FILE 'REGISTRY' ENTERED AT 12:24:55 ON 10 MAY 2004
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
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Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES:     9 MAY 2004  HIGHEST RN 680971-82-8
DICTIONARY FILE UPDATES:    9 MAY 2004  HIGHEST RN 680971-82-8

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2004

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Crossover limits have been increased.  See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more
information enter HELP PROP at an arrow prompt in the file or refer
to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

=> d que l1 ;d l1
L1             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  "POLYETHYLENE GLYCOL"/CN



L1   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2004 ACS on STN
RN   25322-68-3  REGISTRY
CN   Poly(oxy-1,2-ethanediyl), α-hydro-ω-hydroxy- (9CI)  (CA INDEX
     NAME)
OTHER NAMES:
CN   α,ω-Hydroxypoly(ethylene oxide)
CN   α-Hydro-ω-hydroxypoly(oxy-1,2-ethanediyl)
CN   α-Hydro-ω-hydroxypoly(oxyethylene)
CN   1,2-Ethanediol, homopolymer
CN   1660O
CN   1660S
CN   400DAB8
CN   Alkox
CN   Alkox E 100
CN   Alkox E 130
CN   Alkox E 160
CN   Alkox E 240
CN   Alkox E 30
CN   Alkox E 45
CN   Alkox E 60
CN   Alkox E 75
CN   Alkox R 1000
CN   Alkox R 15
CN   Alkox R 150
CN   Alkox R 400
CN   Alkox SR
CN   Antarox E 4000
CN   Aquacide III
CN   Aquaffin
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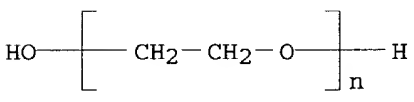
CN Badimol
CN BDH 301
CN Bradsyn PEG
CN Breox 2000
CN Breox 20M
CN Breox 4000
CN Breox 550
CN Breox PEG 300
CN CAFO 154
CN Carbowax
CN Carbowax 100
CN Carbowax 1000
CN Carbowax 1350
CN Carbowax 14000
CN Carbowax 1450
CN Carbowax 1500
CN Carbowax 1540
CN Carbowax 20
CN Carbowax 200
CN Carbowax 20000
CN Carbowax 25000
CN Carbowax 300
CN Carbowax 3350
CN Carbowax 400
CN Carbowax 4000
CN Carbowax 4500
CN **Polyethylene glycol**
ADDITIONAL NAMES NOT AVAILABLE IN THIS FORMAT - Use FCN, FIDE, or ALL for DISPLAY
AR 9002-90-8
DR 615575-04-7, 12676-74-3, 12770-93-3, 9081-95-2, 9085-02-3, 9085-03-4, 54510-95-1, 125223-68-9, 54847-64-2, 59763-40-5, 64441-68-5, 64640-28-4, 133573-31-6, 25104-58-9, 25609-81-8, 134919-43-0, 101677-86-5, 99264-61-6, 106186-24-7, 112895-21-3, 114323-93-2, 50809-04-6, 50809-59-1, 119219-06-6, 60894-12-4, 61840-14-0, 37361-15-2, 112384-37-9, 70926-57-7, 75285-02-8, 75285-03-9, 77986-38-0, 150872-82-5, 154394-38-4, 79964-26-4, 80341-53-3, 85399-22-0, 85945-29-5, 90597-70-9, 88077-80-9, 88747-22-2, 34802-42-1, 107502-63-6, 107529-96-4, 116549-90-7, 156948-19-5, 169046-53-1, 188364-77-4, 188924-03-0, 189154-62-9, 191743-71-2, 201163-43-1, 206357-86-0, 221638-71-7, 225502-44-3, 270910-26-4, 307928-07-0, 356055-70-4, 391229-98-4
MF (C2 H4 O)n H2 O
CI PMS, COM
PCT Polyether
LC STN Files: ANABSTR, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CBNB, CHEMCATS, CHEMLIST, CIN, CSCHEM, CSNB, DETHERM*, EMBASE, IFICDB, IFIPAT, IFIUDB, MEDLINE, PDLCOM*, RTECS*, SPECINFO, USPAT2, USPATFULL, VTB
(*File contains numerically searchable property data)
Other Sources: DSL**, TSCA**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

74270 REFERENCES IN FILE CA (1907 TO DATE)
18731 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
74378 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> d que l3 ;d l3
L3 1 SEA FILE=REGISTRY ABB=ON PLU=ON 215647-85-1

L3 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2004 ACS on STN
RN **215647-85-1** REGISTRY
CN Interferon α-2b (human), pegylated (9CI) (CA INDEX NAME)
OTHER NAMES:
CN Peginterferon alfa-2b
CN PegIntron
CN Sch 54031
MF Unspecified
CI MAN
SR US Adopted Names Council (USAN)
LC STN Files: ADISINSIGHT, BIOSIS, BIOTECHNO, CA, CAPLUS, EMBASE, IPA, PROUSDDR, TOXCENTER, USAN

? OK, name.

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
38 REFERENCES IN FILE CA (1907 TO DATE)
38 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> fil caplus
FILE 'CAPLUS' ENTERED AT 12:25:11 ON 10 MAY 2004
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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FILE COVERS 1907 - 10 May 2004 VOL 140 ISS 20
FILE LAST UPDATED: 9 May 2004 (20040509/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> d que nos l28
L1 1 SEA FILE=REGISTRY ABB=ON PLU=ON "POLYETHYLENE GLYCOL"/CN
L3 1 SEA FILE=REGISTRY ABB=ON PLU=ON 215647-85-1
L5 99849 SEA FILE=CAPLUS ABB=ON PLU=ON L1 OR PEG/OBI OR PEGYLAT?/OBI OR POLYETHYLENE GLYCOL/OBI
L6 64905 SEA FILE=CAPLUS ABB=ON PLU=ON L3 OR INTERFERON?/OBI

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L7         98485 SEA FILE=CAPLUS ABB=ON  PLU=ON  CONJUGAT?/OBI
L8           105 SEA FILE=CAPLUS ABB=ON  PLU=ON  L5 (L) L6 (L)  L7
L9         24364 SEA FILE=CAPLUS ABB=ON  PLU=ON  DI PEPTIDE? OR DIPEPTIDE? OR
                 MET(2W) NLE OR MET (2W) ALA OR GLN(2W) GLY OR ASP (2W)PRO
L10         2400 SEA FILE=CAPLUS ABB=ON  PLU=ON  METHIONINE (2W) NORLEUCINE OR
                 METHIONINE (2W) ALANINE OR GLUTAMINE (2W) GLYCINE OR ASPARTIC
                 ACID (2W) PROLINE
L11            1 SEA FILE=CAPLUS ABB=ON  PLU=ON  L8 AND (L9 OR L10)
L12            3 SEA FILE=CAPLUS ABB=ON  PLU=ON  L5 (L) L7 (L) (L9 OR L10)
L13           18 SEA FILE=CAPLUS ABB=ON  PLU=ON  L5 (L) (L9 OR L10)
L14            6 SEA FILE=CAPLUS ABB=ON  PLU=ON  L13 AND DERIV?
L15            8 SEA FILE=CAPLUS ABB=ON  PLU=ON  L11 OR L12 OR L14
L27            9 SEA FILE=CAPLUS ABB=ON  PLU=ON  L5 AND L6 AND (L9 OR L10)
L28           16 SEA FILE=CAPLUS ABB=ON  PLU=ON  L15 OR L27


=> d .ca l28 1-16

L28  ANSWER 1 OF 16  CAPLUS  COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER:         2004:41229  CAPLUS
DOCUMENT NUMBER:          140:105266
TITLE:                    Boroproline compound combination therapy for various
                          diseases
INVENTOR(S):              Adams, Sharlene; Miller, Glenn T.; Jesson, Michael I.;
                          Jones, Barry
PATENT ASSIGNEE(S):       Point Therapeutics, Inc., USA
SOURCE:                   PCT Int. Appl., 125 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   2
PATENT INFORMATION:

     PATENT NO.        KIND  DATE           APPLICATION NO.  DATE
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     WO 2004004661      A2   20040115       WO 2003-US21547  20030709
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
             CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
             GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
             LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM,
             PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN,
             TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG,
             KZ, MD, RU, TJ
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG,
             CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC,
             NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ,
             GW, ML, MR, NE, SN, TD, TG
     US 2004077601      A1   20040422       US 2003-616694   20030709
PRIORITY APPLN. INFO.:                     US 2002-394856P  P  20020709
                                           US 2002-414978P  P  20021001
                                           US 2003-466435P  P  20030428

GI
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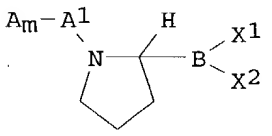


I

searched by Alex Waclawiw

AB A method is provided for treating subjects with combination therapy including compds. of Formula I (wherein m is an integer between 0 and 10, inclusive; A and A1 may be L- or D-amino acid residues, the C bonded to B is in the L-configuration, and each X1 and X2 is, independently, a hydroxy group or a group capable of being hydrolyzed to a hydroxy group in aqueous solution at physiol. pH). It was surprisingly discovered that this combination enhanced the efficacy of both agents, and that administration of Formula I compds. induced cytokine and chemokine production in vivo. The combinations can be used to enhanced ADCC, stimulate immune responses and /or patient and treat certain disorders. The invention also relates to kits and compns. relating to such combinations.

IC ICM A61K

CC 1-7 (Pharmacology)

IT Transcription factors
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(IRF-4 (**interferon** regulatory factor 4); boroproline compound combination therapy for various diseases)

IT **Interferons**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**pegylated** IFN; boroproline compound combination therapy for various diseases)

IT **Interferons**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(α, IFNα; boroproline compound combination therapy for various diseases)

IT **Interferons**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(α-2b; boroproline compound combination therapy for various diseases)

IT **Interferons**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(β; boroproline compound combination therapy for various diseases)

IT **Interferons**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(γ; boroproline compound combination therapy for various diseases)

IT 3424-98-4 4428-95-9 9002-10-2, Tyrosinase 9035-74-9, Glycogen phosphorylase 19545-26-7, KY 12420 19600-01-2, GM2 ganglioside 31362-50-2, Bombesin 36791-04-5, Ribavirin 53678-77-6, Muramyl **dipeptide** 59277-89-3, Acyclovir 62010-37-1, Ganglioside GD3 62010-37-1D, Ganglioside GD3, mimic 65988-71-8, Ganglioside GD2 69521-94-4, Thymosin α-1 80043-53-4, Gastrin-releasing peptide 82410-32-0, Ganciclovir 82707-54-8, Neprilysin 92562-88-4 104227-87-4, Famciclovir 126775-97-1, Campath 127464-60-2, Vascular endothelial growth factor 127759-89-1, Lobucavir 134678-17-4, Lamivudine 139442-47-0, LFM-A 12 142217-69-4, Entecavir 142340-99-6, Adefovir dipivoxil 143491-57-0, Emtricitabine 147014-97-9, Cdk4 kinase 149565-66-2, Kallikrein 6 149682-77-9 152121-44-3 152923-56-3, Daclizumab 156586-89-9, Panorex 163252-36-6, Clevudine 164301-51-3, CNI-1493 167869-21-8, PD98059 170277-31-3, Infliximab 174722-31-7, Rituxan 180288-69-1, Herceptin 183319-69-9, OSI-774 184475-35-2, Iressa 185243-69-0, Etanercept 188039-54-5, Palivizumab 192391-48-3, Bexxar 205923-56-4, IMC-C225 206181-63-7, Zevalin 208921-02-2,

Tositumomab 211555-05-4, WHI-P97 213327-37-8, Oregovomab
216503-57-0, Alemtuzumab 216503-58-1, BEC2 216974-75-3, Avastin
220578-59-6, Mylotarg 334993-12-3, Kallikrein 10 339150-51-5, CeaVac
339150-82-2, LymphoCide 339151-95-0, MDX-22 339151-96-1, MDX-447
339152-71-5, MDX-210 339286-23-6, Gliomab-H 339286-24-7, GNI-250
339526-06-6, B3 (Antibody) 339526-30-6, MDX-220 478159-73-8, BR 96
645405-72-7 645409-76-3 645416-54-2, AG 1458 646031-42-7, Celogovab
646032-07-7, Zamyl
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
(Biological study); USES (Uses)
(boroproline compound combination therapy for various diseases)

L28 ANSWER 2 OF 16 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:41226 CAPLUS
DOCUMENT NUMBER: 140:105321
TITLE: Methods and compositions relating to isoleucine boroproline compounds
INVENTOR(S): Adams, Sharlene; Miller, Glenn T.; Jesson, Michael I.; Jones, Barry
PATENT ASSIGNEE(S): Point Therapeutics, Inc., USA
SOURCE: PCT Int. Appl., 152 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004004658	A2	20040115	WO 2003-US21405	20030709
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2004077601	A1	20040422	US 2003-616694	20030709

PRIORITY APPLN. INFO.: US 2002-394856P P 20020709
US 2002-414978P P 20021001
US 2003-466435P P 20030428

ND

OTHER SOURCE(S): MARPAT 140:105321

AB A method for treating subjects with, inter alia, abnormal cell proliferation or infectious disease using agents of formula (I, AmNHCH(CH(CH3)CH2CH3)COA1R) (where Am and A1 are amino acids and R = organo boronates, organo phosphonates, fluoroalkyl ketones, alphaketos, N-peptiolyl-O-(acylhydroxylamines), azapeptides, azetidines, fluoroolefins **dipeptide** isosteres, peptidyl (α-aminoalkyl) phosphonate esters, aminoacyl pyrrolidine-2-nitriles and 4-cyanothiazolidides) is claimed. Methods for stimulating an immune response using the compds. of the invention are also claimed. Compns. containing Ile-boroPro compds. are also provided as are kits containing the compns. The invention embraces the use of these compds. alone or in combination with other therapeutic agents.

IC ICM A61K
CC 1-12 (Pharmacology)

Section cross-reference(s): 15

IT **Interferons**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**pegylated interferons**; therapeutic methods and compns. relating to isoleucine boroproline compds. alone or in combination with other drugs, antibodies, or antigens)

IT Alums
Antibodies
Antigens
CD1 (antigen)
CD20 (antigen)
CD22 (antigen)
CD26 (antigen)
CD4 (antigen)
Carcinoembryonic antigen
Epidermal growth factor receptors
Glucocorticoids
Immunoglobulins
Interferons
Interleukins
Nucleosides, biological studies
Prostate-specific antigen
Sulfonamides
TCR (T cell receptors)
Vascular endothelial growth factor receptors
neu (receptor)
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(therapeutic methods and compns. relating to isoleucine boroproline compds. alone or in combination with other drugs, antibodies, or antigens)

IT **Interferons**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(α, IFNα-2b; therapeutic methods and compns. relating to isoleucine boroproline compds. alone or in combination with other drugs, antibodies, or antigens)

IT **Interferons**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(α-2a; therapeutic methods and compns. relating to isoleucine boroproline compds. alone or in combination with other drugs, antibodies, or antigens)

IT **Interferons**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(α-2b; therapeutic methods and compns. relating to isoleucine boroproline compds. alone or in combination with other drugs, antibodies, or antigens)

IT **Interferons**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(α1b; therapeutic methods and compns. relating to isoleucine boroproline compds. alone or in combination with other drugs, antibodies, or antigens)

IT **Interferons**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(α; therapeutic methods and compns. relating to isoleucine boroproline compds. alone or in combination with other drugs, antibodies, or antigens).

IT **Interferons**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(αn3; therapeutic methods and compns. relating to isoleucine boroproline compds. alone or in combination with other drugs, antibodies, or antigens)

IT 6576-51-8, Stallimycin hydrochloride 6591-72-6, Penicillin v hydrabamine 6804-07-5, Carbadox 6981-18-6, Ormetoprim 6990-06-3, Fusidic acid 7054-25-3, Quinidine gluconate 7179-50-2, Oxytetracycline calcium 7481-89-2, Zalcitabine 7527-91-5, Acrisorcin 7542-37-2, Paromomycin 7681-11-0, Potassium iodide, biological studies 7681-93-8, Natamycin 8017-57-0D, Trisulfapyrimidine, derivs. 8025-81-8, Spiramycin 8063-07-8, Kanamycin 8063-91-0, Mirincamycin hydrochloride 8064-90-2 8068-28-8, Colistimethate sodium 9001-06-3, Chitinase 9015-68-3, Asparaginase 9041-93-4, Bleomycin sulfate 10118-85-1, Lydimycin 10118-90-8, Minocycline 10500-82-0, Famotine hydrochloride 10540-97-3, Memotine hydrochloride 11006-76-1, Virginiamycin 11006-77-2, Statolon 11015-37-5, Bambermycin 11016-07-2, Fungimycin 11033-34-4, Steffimycin 11048-13-8, Nebramycin 11048-15-0, Kalafungin 11051-71-1, Avilamycin 11056-09-0, Ranimycin 11056-11-4, Biniramycin 11056-12-5, Cirolemycin 11056-13-6, Denofungin 11056-18-1, Scopafungin 11056-20-5, Zorbamycin 11078-21-0, Filipin 11096-49-4, Partricin 11096-79-0, Alamecin 11111-12-9, Cephalosporin 11121-32-7, Mepartricin 13292-46-1, Rifampin 13292-46-1D, Rifampin, derivs. 13392-28-4, Rimantadine 13411-16-0, Nifurpirinol 13463-41-7, Pyrithione zinc 13614-98-7, Minocycline hydrochloride 14088-71-2, Proclonol 14698-29-4, Oxolinic acid 15037-55-5, Ethonam nitrate 15176-29-1, Edoxudine 15318-45-3, Thiamphenicol 15475-56-6, Methotrexate sodium 15663-27-1, Cisplatin 15686-71-2, Cephalexin 16037-91-5, Stibogluconate sodium 16846-24-5, Josamycin 16915-79-0, Mequidox 17090-79-8, Monensin 17230-86-3, Carbenicillin potassium 17692-15-8, Furazolium tartrate 17784-12-2, Sulfacytine 18323-44-9, Clindamycin 19387-91-8, Tinidazole 19561-70-7, Nifuratrone 19885-51-9, Aranotin 20685-78-3, Rolitetracycline nitrate 21462-39-5, Clindamycin hydrochloride 21593-23-7, Cephapirin 21638-36-8, Nifurimide 21649-57-0, Carbenicillin phenylsodium 21679-14-1, Fludarabine 21736-83-4, Spectinomycin hydrochloride 21738-42-1, Oxamniquine 22204-24-6, Pyrantel pamoate 22373-78-0, Monensin sodium 22484-64-6, Sulfanilate zinc 22573-93-9, Alexidine 22832-87-7, Miconazole nitrate 22916-38-7, Orconazole nitrate 22916-47-8, Miconazole 22994-85-0, Benznidazole 23067-13-2, Erythromycin gluceptate 23155-02-4, Fosfomycin 23214-92-8, Doxorubicin 23239-41-0, Cephacetrile sodium 23256-30-6, Nifurtimox 23313-80-6, Epitetracycline hydrochloride 23319-48-4, Megalomicin potassium phosphate 23444-86-2, Suncillin sodium 23541-50-6, Daunorubicin hydrochloride 23593-75-1, Clotrimazole 23736-58-5, Cloxacillin benzathine 24169-02-6, Econazole nitrate 24356-60-3, Cephapirin sodium 24390-14-5, Doxycycline hyclate 24729-96-2, Clindamycin phosphate 25316-40-9, Doxorubicin hydrochloride 25389-94-0, Kanamycin sulfate 25507-04-4, Clindamycin palmitate hydrochloride 25526-93-6, Alovudine 25953-19-9, Cefazolin 26309-95-5, Pivampicillin hydrochloride 26605-69-6, Carbenicillinindanylsodium 26774-90-3, Epicillin 26786-84-5, Lomofungin 26787-78-0, Amoxicillin 27164-46-1, Cefazolin sodium 27220-47-9, Econazole 27523-40-6, Isoconazole 27591-69-1, Tilorone hydrochloride 27762-78-3, Kethoxal 27823-62-7, Chlortetracycline bisulfate 27877-51-6, Tolindate 28069-65-0, Cuprimyxin 28088-64-4, Aminosalicylic acid 28657-80-9, Cinoxacin 29342-05-0, Ciclopirox 29457-07-6, Ticarcillin disodium 29767-20-2, Teniposide 29984-33-6, Vidarabine phosphate 30034-03-8, Cefamandole sodium 30516-87-1, Zidovudine 31342-36-6, Chloramphenicol pantothenate complex

31431-39-7, Mebendazole 32385-11-8, Sisomicin 32886-97-8, Amdinocillin pivoxil 32887-01-7, Amdinocillin 32986-56-4, Tobramycin 33069-62-4, Taxol 33419-42-0, Etoposide 33564-30-6, Cefoxitin sodium 34444-01-4, Cefamandole 35523-45-6, Fludalanine 35554-44-0, Enilconazole 35607-20-6, Avridine 35607-66-0, Cefoxitin 35834-26-5, Rosaramicin 36791-04-5, Ribavirin 36983-81-0, Fosfonet sodium 37091-65-9, Azlocillin sodium 37091-66-0, Azlocillin 37321-09-8, Apramycin 37332-99-3, Avoparcin 37338-39-9 37517-28-5, Amikacin 37661-08-8, Bacampicillin hydrochloride 38070-41-6, Tiodonium chloride 38821-53-3, Cephradine 39030-72-3, Pivampicillin pamoate 39809-25-1, Penciclovir 39831-55-5, Amikacin sulfate 39878-70-1, Talampicillin hydrochloride 40034-42-2, Rosoxacin 40966-79-8, Sarpicillin 41575-94-4, Carboplatin 41621-49-2, Ciclopirox olamine 42057-22-7, Mezlocillin sodium 42190-91-0, Pivampicillin probenate 42540-40-9, Cefamandole nafate 42835-25-6, Flumequine 43143-11-9, Bispyrithione magsulfex 43169-50-2, Betamicin sulfate 49620-13-5, Robustaflavone 49842-07-1, Tobramycin sulfate 50370-12-2, Cefadroxil 50838-36-3, Tolciclate 51022-98-1, Butirosin sulfate 51481-64-2, Rosaramicin propionate 51481-65-3, Mezlocillin 51547-64-9, Rosaramicin stearate 51627-14-6, Cefatrizine 51627-20-4, Cefaparole 51762-05-1, Cefroxadine 52123-49-6, Cefazaflur sodium 52152-93-9, Cefsulodin sodium 53066-26-5, Lexithromycin 53179-09-2, Sisomicin sulfate 53230-10-7, Mefloquine 53678-77-6, Muramyl **dipeptide** 53808-87-0, Tetroxoprim 53910-25-1, Pentostatin 53994-73-3, Cefaclor 54965-21-8, Albendazole 55103-30-5, Rosaramicin butyrate 55162-26-0, Pirbenicillin sodium 55242-74-5, Oxifungin hydrochloride 55242-77-8, Triafungin 55268-74-1, Praziquantel 55268-75-2, Cefuroxime 55298-68-5, Neomycin palmitate 55694-87-6, Pentizidone sodium 55852-84-1, Bacitracin methylene disalicylate 56093-45-9, Selenium sulfide 56219-57-9, Arildone 56238-63-2, Cefuroxime sodium 56390-09-1, Epirubicin hydrochloride 56391-57-2, Netilmicin sulfate 56433-46-6, Cetocycline hydrochloride 56585-33-2, Trimethoprim sulfate 56689-42-0, Repromicin 56796-20-4, Cefmetazole 56796-39-5, Cefmetazole sodium 57363-13-0, Droxacin sodium 57852-57-0, Idarubicin hydrochloride 58001-44-8, Clavulanic acid 58152-03-7, Isepamicin 58795-03-2, Apalcillin sodium 58857-02-6, Ambruticin 58944-73-3, Sinefungin 59070-06-3, Ticarcillin cresylsodium 59277-89-3, Acyclovir 59695-59-9, Cephalexin hydrochloride 59703-84-3, Piperacillin sodium 59733-86-7, Butikacin 59794-18-2, Paulomycin 59831-63-9, Doconazole 60207-31-0, Azaconazole 60628-96-8, Bifonazole 60802-40-6, Rosaramicin sodium phosphate 60925-61-3, Ceforanide 61036-62-2, Teicoplanin 61270-78-8, Cefonicid sodium 61318-91-0, Sulconazole nitrate 61379-65-5, Rifapentine 61477-96-1, Piperacillin 62013-04-1, Dirithromycin 62587-73-9, Cefsulodin 62893-19-0, Cefoperazone 62893-20-3, Cefoperazone sodium 62973-77-7, Parconazole hydrochloride 63198-97-0, Viroxime 63527-52-6, Cefotaxime 63585-09-1, Foscarnet sodium

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(therapeutic methods and compns. relating to isoleucine boroproline compds. alone or in combination with other drugs, antibodies, or antigens)

L28 ANSWER 3 OF 16 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:777368 CAPLUS

DOCUMENT NUMBER: 139:281211

TITLE: Polymer compositions comprising antifibrotic agents, and methods of treatment, pharmaceutical compositions, and methods of preparation therefor

INVENTOR(S): Poiani, George; Riley, David; Kohn, Joachim; Kemnitzer, John E.

PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 53 pp., Cont.-in-part of U.S. 6,517,824.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003186869	A1	20031002	US 2002-285270	20021030
US 5219564	A	19930615	US 1991-726301	19910705
US 5372807	A	19941213	US 1992-934818	19920824
US 5455027	A	19951003	US 1993-23069	19930225
US 5720950	A	19980224	US 1994-260080	19940615
US 5660822	A	19970826	US 1995-479150	19950607
US 6517824	B1	20030211	US 1996-650324	19960520

PRIORITY APPLN. INFO.:
US 1990-523232 B1 19900514
US 1990-549494 B1 19900706
US 1991-726301 A1 19910705
US 1992-864361 B2 19920406
US 1992-934818 A3 19920824
US 1994-260080 A3 19940615
US 1995-479150 A2 19950607
US 1996-650324 A2 19960520
US 1997-864361 B2 19970406

AB A method for treating pulmonary hypertension and other diseases involving a defect in collagen metabolism, by administration of an effective amount of a liposome encapsulated copolymer conjugate antifibrotic composition, is disclosed. The antifibrotic agents comprise conjugates of proline analogs, such as cis-4-hydroxy-L-proline (CHOP), 3,4-dehydro-DL-proline (DHP), (R)-(-)-2-thiazolidine-4-carboxylic acid (THP), and (S)-(-)-2-azetidinecarboxylic acid (ACA) and polyethylene glycol. Consistent, high loadings (>90%) of the antifibrotic agent are achieved by first forming a dipeptide with L-lysine, after which the dipeptide is copolymd. with the polymer component to form the copolymer conjugate. The polymer is preferably poly(ethylene glycol) having a weight average mol. weight of from about 500 to about 15,000. Efficient delivery and consistent release of the antifibrotic agent inhibits collagen accumulation and treats the diseases involved. Accordingly, there is a substantial reduction in the quantity of antifibrotic agent necessary, and thus a corresponding reduction in the potential for toxicity that would otherwise result from its prolonged administration.

IC ICM A61K038-16
ICS A61K038-08; A61K038-06; A61K038-10
NCL 514012000; 514013000; 514014000; 514015000; 514016000; 514017000; 514018000; 514019000
CC 63-5 (Pharmaceuticals)
IT **Dipeptides**
RL: IMF (Industrial manufacture); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(**conjugates** with **polyethylene glycol**; polymer compns. comprising antifibrotic agents, and methods of treatment, pharmaceutical compns., and methods of preparation therefor)
IT Polyoxyalkylenes, biological studies
RL: IMF (Industrial manufacture); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(conjugates with proline analogs or **derivs.**; polymer compns.

comprising antifibrotic agents, and methods of treatment, pharmaceutical compns., and methods of preparation therefor)

IT 618-27-9DP, cis-4-Hydroxy-L-proline, **dipeptide derivs**., **conjugates** with **polyethylene glycol** 2133-34-8DP, (S)-(-)-2-Azetidinecarboxylic acid, **dipeptide derivs.**, **conjugates** with **polyethylene glycol** 3395-35-5DP, 3,4-Dehydro-DL-proline, **dipeptide derivs.**, **conjugates** with **polyethylene glycol** 25322-68-3DP, Polyethylene glycol, conjugates with proline analogs or **derivs.** 34592-47-7DP, **dipeptide derivs.**, **conjugates** with **polyethylene glycol**
RL: IMF (Industrial manufacture); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(polymer compns. comprising antifibrotic agents, and methods of treatment, pharmaceutical compns., and methods of preparation therefor)

L28 ANSWER 4 OF 16 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:570839 CAPLUS
DOCUMENT NUMBER: 139:116270
TITLE: Enhancing the immunogenicity of carcinoembryonic antigen
INVENTOR(S): Klysner, Steen; Voldborg, Bjorn
PATENT ASSIGNEE(S): Pharmexa A/S, Den.
SOURCE: PCT Int. Appl., 140 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003059379	A2	20030724	WO 2003-DK31	20030117
WO 2003059379	A3	20031204		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EE, EE, ES, FI, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: DK 2002-82 A 20020117
US 2002-350047P P 20020117

AB The authors disclose methods for immunizing actively against autologous carcinoembryonic antigen (CEA). The method comprises CEA variants which are either administered as a protein vaccine or by nucleic acid vaccination or live/viral vaccination. Preferred embodiments include immunization with variants that include at least one foreign T-helper epitope introduced in the CEA sequence. Disclosed are variant proteins, DNA, vectors, and host cells useful for practicing the method.

IC ICM A61K039-00
CC 15-2 (Immunochemistry)
Section cross-reference(s): 2, 3, 14, 63

IT **Interferons**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(γ; for enhancing immunogenicity of carcinoembryonic antigen variants)

IT 99-20-7D, Trehalose, esters with mycolic acids 3700-67-2 53678-77-6, Muramyl **dipeptide** 66594-14-7, Quil A 83869-56-1, GM-CSF 141256-04-4, QS21
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(for enhancing immunogenicity of carcinoembryonic antigen variants)

IT 111-02-4, Squalene 9004-54-0, Dextran, biological studies 9005-25-8, Starch, biological studies **25322-68-3**, **Polyethylene glycol**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(in delivery of immunogenic carcinoembryonic antigen variants)

L28 ANSWER 5 OF 16 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:356466 CAPLUS
DOCUMENT NUMBER: 138:374161
TITLE: Biocompatible polymers including peptide spacer
INVENTOR(S): Park, Myung-Ok
PATENT ASSIGNEE(S): Biopolymed Inc., S. Korea
SOURCE: PCT Int. Appl., 47 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003037915	A1	20030508	WO 2002-KR2036	20021031
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2003185798	A1	20031002	US 2003-380498	20030314

PRIORITY APPLN. INFO.: KR 2001-67369 A 20011031
WO 2002-KR2036 W 20021031

AB The present invention relates to new biocompatible polymer derivs. including peptide spacers and their methods of preparation The present invention also relates to the conjugates formed by covalent or non-covalent bonding and their methods of preparation These biocompatible polymers with peptide spacers providing regions of hydrophobicity and pos. charge can enhance their interaction with cell membrane to increase the cell trafficking, endosomal disruption, the circulation half-life in blood, and the stability of conjugated therapeutic drug. For example, (mPEG12000-OCH2CO-Gly-Gly)2 (2,4-diaminobutyric acid)-Gly-COOH was prepared and conjugated with paclitaxel.

IC ICM C07K002-00
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1, 34, 35

IT **Interferons**
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(**conjugates** with peptide-containing **PEG** derivative; preparation

of biocompatible polymers containing peptide spacer for drug delivery)

IT **Dipeptides**
Polyesters, reactions
Polyoxyalkylenes, reactions
Polyphosphazenes
Polysaccharides, reactions
Polyurethanes, reactions
Tripeptides
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of biocompatible polymers containing peptide spacer for drug delivery)

IT 56-40-6, Glycine, reactions 305-62-4, 2,4-Diaminobutyric acid 556-50-3 657-27-2, L-Lysine hydrochloride 3253-17-6 9002-89-5, Polyvinyl alcohol 9003-01-4, Polyacrylic acid 9003-05-8, Polyacrylamide 9003-39-8, Polyvinylpyrrolidone 9004-54-0, Dextran, reactions 25104-18-1, Poly(L-lysine) **25322-68-3**, **Polyethylene glycol** 25322-69-4, Polypropylene glycol 26023-30-3, Poly[oxy(1-methyl-2-oxo-1,2-ethanediyl)] 26100-51-6, Polylactic acid 38000-06-5, Poly(L-lysine) 122037-91-6 124661-64-9 139729-28-5 345260-48-2, Polytrimethylene glycol
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of biocompatible polymers containing peptide spacer for drug delivery)

IT 7689-03-4DP, Camptothecin, conjugates with peptide-containing **PEG** derivative 33069-62-4DP, Paclitaxel, conjugates with peptide-containing **PEG** derivative 143011-72-7DP, G-CSF, conjugates with peptide-containing **PEG** derivative 521098-55-5DP, conjugates with camptothecin 521098-56-6DP, conjugates with paclitaxel 521098-57-7DP, conjugates with protein drugs
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of biocompatible polymers containing peptide spacer for drug delivery)

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L28 ANSWER 6 OF 16 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:977700 CAPLUS
DOCUMENT NUMBER: 138:44733
TITLE: Dry powder inhalation system for transpulmonary administration
INVENTOR(S): Yamashita, Chikamasa; Ibaragi, Shigeru; Fukunaga, Yuichiro; Akagi, Akitsuna
PATENT ASSIGNEE(S): Otsuka Pharmaceutical Co., Ltd., Japan
SOURCE: PCT Int. Appl., 121 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002102445	A1	20021227	WO 2002-JP5955	20020614

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

EE 200400011 A 20040216 EE 2004-11 20020614

EP 1402913 A1 20040331 EP 2002-736105 20020614

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR

PRIORITY APPLN. INFO.: JP 2001-182504 A 20010615

JP 2001-400871 A 20011228

JP 2002-111131 A 20020412

WO 2002-JP5955 W 20020614

AB It is intended to provide a novel dry powder inhalation system for transpulmonary administration. This dry powder inhalation system for transpulmonary administration contains a single dose of the active ingredient and is characterized by comprising a combination of a container packed with a freeze-dried composition having the following properties: (i) being in the form of a non-powder cake; (ii) having a decay index of ≥ 0.015; and (iii) upon an air impact having an air speed of at least 1 m/s and an air flow rate of at least 17 mL/s, being disintegrated into fine particles having an average particle diameter of ≤ 10 μm or an effective particle ratio of ≥ 10%; with a device provided with means of imparting the above air impact to the freeze-dried composition in the above container and means of discharging the powdery freeze-dried composition having been disintegrated into fine particles from the container. A freeze-dried cake was prepared from interferon-α and isoleucine, and applied to an inhaler of the present invention for transpulmonary powder administration.

IC ICM A61M015-00

ICS A61K009-12; A61K009-72

CC 63-6 (Pharmaceuticals)

ST inhalant powder transpulmonary; **interferon** freeze dried transpulmonary inhalant

IT Amino acids, biological studies

Carbohydrates, biological studies

Dipeptides

Polyoxyalkylenes, biological studies

Tripeptides

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses) (carriers; dry powder inhalation system for transpulmonary administration)

IT **Interferons**

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses) (α; dry powder inhalation system for transpulmonary administration)

IT **Interferons**

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses) (γ; dry powder inhalation system for transpulmonary administration)

IT 56-12-2, biological studies 56-40-6, Glycine, biological studies 56-41-7, Alanine, biological studies 61-90-5, Leucine, biological studies 63-42-3, Lactose 63-91-2, Phenylalanine, biological studies 69-65-8, D-Mannitol 72-18-4, Valine, biological studies 73-32-5, Isoleucine, biological studies 107-35-7, Taurine 107-95-9, β-Alanine 1002-62-6, Sodium caprate 1119-34-2, Arginine hydrochloride 7585-39-9, β-Cyclodextrin **25322-68-3**, **Polyethylene glycol**

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses) (carriers; dry powder inhalation system for transpulmonary administration)

REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L28 ANSWER 7 OF 16 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:716321 CAPLUS
DOCUMENT NUMBER: 137:246527
TITLE: Multivalent MHC constructs: Immunoanalysis, diagnosis and therapy
INVENTOR(S): Winther, Lars; Petersen, Lars Oestergaard; Buus, Soeren; Schoeller, Joergen; Ruub, Erik; Aamellem, Oeystein
PATENT ASSIGNEE(S): Dako A/S, Den.; Dynal Biotech Asa
SOURCE: PCT Int. Appl., 304 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002072631	A2	20020919	WO 2002-DK169	20020313
WO 2002072631	C1	20021128		
WO 2002072631	A3	20031106		
W: AE, AG, AL, AM, AT, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EE, EE, ES, FI, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1377609	A2	20040107	EP 2002-706685	20020313
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
NO 2003004020	A	20031106	NO 2003-4020	20030911

PRIORITY APPLN. INFO.:

DK 2001-435	A	20010314
DK 2001-436	A	20010314
DK 2001-441	A	20010314
US 2001-275447P	P	20010314
US 2001-275448P	P	20010314
US 2001-275470P	P	20010314
WO 2002-DK169	W	20020313

AB The authors disclose MHC mol. constructs (classical and non-classical) conjugated to soluble or insol. carriers wherein the affinity and avidity of the constructs exceed that of comparable MHC tetramers. In one example, the construct is comprised of biotinylated HLA-A2 bound to FITC-labeled streptavidin conjugated to soluble derivatized dextran. The above construct loaded with MART-1 or influenza virus peptides was shown to effect T-cell activation at a lower concentration than. Also comprised by the present invention is the sample-mounted use of MHC mols., MHC mol. multimers, and MHC mol. constructs.

IC ICM C07K014-705
CC 15-2 (Immunochemistry)
Section cross-reference(s): 1, 8, 63
IT **Interferons**
RL: ARG (Analytical reagent use); BPN (Biosynthetic preparation); DGN (Diagnostic use); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); PREP (Preparation); USES (Uses)

(α; of multivalent constructs of MHC antigens for immunoanal., diagnosis, and therapy)

IT **Interferons**
RL: ARG (Analytical reagent use); BPN (Biosynthetic preparation); DGN (Diagnostic use); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); PREP (Preparation); USES (Uses)
(β; of multivalent constructs of MHC antigens for immunoanal., diagnosis, and therapy)

IT **Interferons**
RL: ARG (Analytical reagent use); BPN (Biosynthetic preparation); DGN (Diagnostic use); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); PREP (Preparation); USES (Uses)
(γ; of multivalent constructs of MHC antigens for immunoanal., diagnosis, and therapy)

IT 1398-61-4P, Chitin 9000-07-1P, Carrageenan 9000-30-0P, Guaran 9002-89-5P, Poly(vinyl alcohol) 9002-98-6P 9003-01-4P, Poly(acrylic acid) 9003-11-6P, Ethylene oxide-propylene oxide copolymer 9004-30-2P, Carboxymethyl hydroxyethyl cellulose 9004-32-4P, Carboxymethyl cellulose 9004-34-6DP, Cellulose, derivs. 9004-54-0DP, Dextran, polyaldehydes, biological studies 9004-62-0P, Hydroxyethyl cellulose 9005-25-8DP, Starch, hydroxylated 9005-27-0P, Hydroxyethyl starch 9005-32-7P, Alginic acid 9011-14-7P, Poly(methyl methacrylate) 9012-36-6P, Agarose 9012-76-4P, Chitosan 9032-36-4P 9044-05-7DP, Carboxymethyl dextran, lactones 9044-05-7P, Carboxymethyl dextran 9049-76-7P, Hydroxypropyl starch 9050-67-3P, Schizophyllan 9057-02-7P, Pullulan 11138-66-2P, Xanthan 12619-70-4P, Cyclodextrin 24937-72-2P, Poly(maleic anhydride) 25087-26-7P, Poly(methacrylic acid) 25104-18-1P, Polylysine 25249-16-5P, Poly(2-hydroxy ethyl methacrylate) **25322-68-3P**, **Polyethylene glycol** 25322-69-4P, Polypropylene glycol 25513-46-6P, Polyglutamic acid 25702-74-3P, Ficoll 26099-09-2P, Poly(maleic acid) 28651-69-6P, Vinyl alcohol-vinyl chloroacetate polymer 39385-63-2P, 6-Amino-6-deoxy cellulose 39464-87-4P, Scleroglucan 52108-64-2P, 6-O-Carboxymethyl chitin 83512-85-0P, N-Carboxymethyl chitosan 124586-30-7P, Carboxymethyl ficoll 142804-65-7P, Gellan
RL: ARG (Analytical reagent use); BPN (Biosynthetic preparation); DGN (Diagnostic use); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); PREP (Preparation); USES (Uses)
(as carrier for multivalent constructs of MHC antigens)

IT 53-43-0, DHEA 72-55-9, DDE, biological studies 83-44-3D, alum complexes 7429-90-5D, Aluminum, salts 10103-46-5, Calcium phosphate 18656-38-7, Dimyristoylphosphatidylcholine 26780-50-7, Poly(lactide-co-glycolide) 53678-77-6, Muramyl **dipeptide** 61361-72-6, DMPG 66578-77-6, Adju-Phos 66594-14-7, Quil A 124389-07-7, Muramyl tripeptide 141256-04-4, QS-21 172889-84-8, MF59
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(for vaccines of multivalent constructs of MHC antigens)

L28 ANSWER 8 OF 16 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:184921 CAPLUS
DOCUMENT NUMBER: 136:246375
TITLE: Down-regulation of IgE by vaccination
INVENTOR(S): Klysner, Steen; Von Hoegen, Paul; Voldborg, Bjorn; Gautam, Anand
PATENT ASSIGNEE(S): Pharmexa A/S, Den.
SOURCE: PCT Int. Appl., 151 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002020038	A2	20020314	WO 2001-DK579	20010906
WO 2002020038	A3	20020613		
W: AE, AG, AL, AM, AT, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EE, EE, ES, FI, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2001085721	A5	20020322	AU 2001-85721	20010906
US 2002172673	A1	20021121	US 2001-949375	20010906
EP 1330263	A2	20030730	EP 2001-964944	20010906
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2004508028	T2	20040318	JP 2002-524521	20010906

PRIORITY APPLN. INFO.:			
DK 2000-1326	A	20000906	
US 2000-232831P	P	20000915	
WO 2001-DK579	W	20010906	

AB The authors disclose methods for immunizing against autologous (self) IgE. In particular, the invention discloses methods for inducing cytotoxic T-lymphocytes to B-cells producing autologous IgE. Vaccination may be administered by nucleic acid vaccination or live vaccination. Also disclosed are methods for inducing antibodies reactive with autologous IgE as well as methods for inducing a combined antibody and CTL response specific for IgE.

IC ICM A61K039-00

CC 15-2 (Immunochemistry)
Section cross-reference(s): 2

IT **Interferons**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(α; of immunogen targeting receptors on antigen-presenting cells for inducing immune response against autologous IgE)

IT 3458-28-4D, D-Mannose, immunogen-containing 9004-54-0, Dextran, biological studies 9005-25-8, Starch, biological studies 9036-88-8, Mannan **25322-68-3, Polyethylene glycol** 53678-77-6, Muramyl **dipeptide** 66594-14-7, Quil A 141256-04-4, QS21 307555-09-5, RIBI
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(for targeting antigen-presenting cells with immunogen inducing immune response against autologous IgE)

Applicants

L28 ANSWER 9 OF 16 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER:	2002:1472 CAPLUS
DOCUMENT NUMBER:	137:217336
TITLE:	An improved procedure for the synthesis of branched **polyethylene glycols** (**PEGs**) with the reporter **dipeptide Met** -.beta.**Ala** for protein **conjugation**
AUTHOR(S):	Guiotto, Andrea; Pozzobon, Michela; Sanavio, Chiara; Schiavon, Oddone; Orsolini, Piero; Veronese, Francesco M.
CORPORATE SOURCE:	Dipartimento di Science Farmaceutiche, Padua, 35100, Italy
SOURCE:	Bioorganic & Medicinal Chemistry Letters (2002),

12(2), 177-180
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A new and more efficient route to the synthesis of branched PEG for protein conjugation, bearing a reporter dipeptide Met-βAla, is described, which allows better purification of the final product by ion exchange chromatog. The product has the combined advantages of an 'umbrella-like' branched structure, which allows a better coverage of the protein surface, and the presence of the dipeptide Met-βAla which has been used to detect the position of PEGylation within the peptide sequence.

CC 35-8 (Chemistry of Synthetic High Polymers)

ST **polyethylene glycol dipeptide** protein **conjugation**

IT 159540-80-4
RL: RCT (Reactant); RACT (Reactant or reagent)
(synthesis of branched **polyethylene glycols** with reporter **dipeptide Met**-.beta.**Ala** for protein **conjugation**)

IT 266313-95-5P 452336-19-5P 457604-76-1P
RL: SPN (Synthetic preparation); PREP (Preparation)
(synthesis of branched **polyethylene glycols** with reporter **dipeptide Met**-.beta.**Ala** for protein **conjugation**)

REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L28 ANSWER 10 OF 16 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:136991 CAPLUS
DOCUMENT NUMBER: 134:198075
TITLE: Triglyceride-free compositions and methods for enhanced absorption of hydrophilic therapeutic agents
INVENTOR(S): Patel, Mahesh V.; Chen, Feng-Jing
PATENT ASSIGNEE(S): Lipocine, Inc., USA
SOURCE: PCT Int. Appl., 113 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 12
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001012155	A1	20010222	WO 2000-US18807	20000710
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6309663	B1	20011030	US 1999-375636	19990817
EP 1210063	A1	20020605	EP 2000-947184	20000710
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
JP 2003506476	T2	20030218	JP 2001-516502	20000710

US 2001024658 A1 20010927 US 2000-751968 20001229
US 6458383 B2 20021001
PRIORITY APPLN. INFO.: US 1999-375636 A 19990817
WO 2000-US18807 W 20000710

AB The present invention relates to triglyceride-free pharmaceutical compns., pharmaceutical systems, and methods for enhanced absorption of hydrophilic therapeutic agents. The compns. and systems include an absorption enhancing carrier, where the carrier is formed from a combination of at least two surfactants, at least one of which is hydrophilic. A hydrophilic therapeutic agent can be incorporated into the composition, or can be co-administered with the composition as part of a pharmaceutical system. The invention also provides methods of treatment with hydrophilic therapeutic agents using these compns. and systems. For example, when a composition containing Cremophor RH40 0.30, Arlacel 186 0.20, Na taurocholate 0.18, and propylene glycol 0.32 g, resp., was used, the relative absorption of PEG 4000 as a model macromol. drug was enhanced by 991%.

IC ICM A61K009-00
ICS A61K009-14; A61K009-16; A61K009-20; A61K009-22; A61K009-28; A61K009-48

CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1

IT Phosphatidylethanolamines, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses) (reaction products, with **PEG** and PVP; compns. for enhanced absorption of hydrophilic drugs using combination of surfactants)

IT **Interferons**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses) (α; compns. for enhanced absorption of hydrophilic drugs using combination of surfactants)

IT **Interferons**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses) (β; compns. for enhanced absorption of hydrophilic drugs using combination of surfactants)

IT 50-21-5, Lactic acid, biological studies 50-21-5D, Lactic acid, acyl esters 50-56-6, Oxytocin, biological studies 50-70-4, Sorbitol, biological studies 50-81-7, Ascorbic acid, biological studies 51-15-0, Pralidoxime chloride 51-43-4, Epinephrine 51-55-8, Atropine, biological studies 51-60-5, Neostigmine methyl sulfate 52-24-4, Thiotepa 53-79-2, Puromycin 56-81-5, Glycerol, biological studies 57-10-3, Palmitic acid, biological studies 57-11-4, Stearic acid, biological studies 57-13-6, Urea, biological studies 57-22-7, Vincristine 57-55-6, Propylene glycol, biological studies 57-55-6D, Propylene glycol, ethers 57-64-7, Physostigmine salicylate 57-88-5, Cholesterol, biological studies 57-94-3, Tubocurarine chloride 59-05-2, Methotrexate 60-00-4, EDTA, biological studies 60-00-4D, EDTA, conjugates with antipain and chitosan 60-31-1, Acetylcholine chloride 60-33-3, Linoleic acid, biological studies 62-31-7, Dopamine hydrochloride 63-91-2, Phenylalanine, biological studies 64-18-6, Formic acid, biological studies 64-19-7, Acetic acid, biological studies 65-28-1, Phentolamine mesylate 65-85-0, Benzoic acid, biological studies 66-71-7, 1,10-Phenanthroline 67-42-5, EGTA 68-11-1, Thioglycolic acid, biological studies 68-19-9, Vitamin B12 69-65-8, Mannitol 69-72-7, Salicylic acid, biological studies 69-79-4D, Maltose, alkyl esters 69-93-2, Uric acid, biological studies 70-51-9, Deferoxamine 71-27-2, Suxamethonium chloride 74-89-5, Methanamine, biological studies 75-75-2, Methanesulfonic acid 77-19-0, Dicyclomine 77-92-9, Citric acid, biological studies 77-92-9D, Citric acid, glycerides 79-09-4, Propionic acid, biological studies 79-10-7, Acrylic acid, biological studies 79-10-7D, Acrylic acid, polymers 81-24-3, Taurocholic acid

81-25-4, Cholic acid 83-44-3, Deoxycholic acid 87-69-4, Tartaric acid, biological studies 87-69-4D, Tartaric acid, glycerides 89-57-6, Mesalamine 89-65-6, Isoascorbic acid 101-26-8, Pyridostigmine bromide 102-71-6, Triethanolamine, biological studies 104-15-4, p-Toluenesulfonic acid, biological studies 107-15-3, Ethylenediamine, biological studies 107-21-1, Ethylene glycol, biological studies 107-92-6, Butyric acid, biological studies 110-15-6, Succinic acid, biological studies 110-16-7, Maleic acid, biological studies 110-17-8, Fumaric acid, biological studies 110-27-0, Isopropyl myristate 111-62-6, Ethyl oleate 112-80-1, Oleic acid, biological studies 114-07-8, Erythromycin 114-80-7, Neostigmine bromide 115-77-5, Pentaerythritol, biological studies 121-44-8, Triethylamine, biological studies 122-20-3, Triisopropanolamine 124-04-9, Adipic acid, biological studies 124-07-2, Caprylic acid, biological studies 128-13-2, Ursodeoxycholic acid 129-06-6, Warfarin sodium 131-49-7, Diatrizoate meglumine 138-36-3, p-Bromobenzenesulfonic acid 140-64-7, Pentamidine isethionate 141-22-0, Ricinoleic acid 141-43-5, Ethanolamine, biological studies 142-62-1, Caproic acid, biological studies 142-91-6, Isopropyl palmitate 143-07-7, Lauric acid, biological studies 143-07-7D, Lauric acid, Macrogol glycerides 144-55-8, Sodium hydrogen carbonate, biological studies 144-62-7, Oxalic acid, biological studies 145-42-6, Sodium taurocholate 147-94-4, Cytarabine 148-24-3, 8-Quinolinol, biological studies 151-21-3, Sodium lauryl sulfate, biological studies 151-41-7, Lauryl sulfate 154-21-2, Lincomycin 155-97-5, Pyridostigmine 299-42-3, Ephedrine 334-48-5, Capric acid 360-65-6, Glycodeoxycholic acid 434-13-9, Lithocholic acid 463-40-1, Linolenic acid 463-79-6, Carbonic acid, biological studies 471-34-1, Calcium carbonate, biological studies 474-25-9, Chenodeoxycholic acid 475-31-0, Glycocholic acid 516-35-8, Taurochenodeoxycholic acid 516-50-7, Taurodeoxycholic acid 526-95-4, Gluconic acid 541-15-1D, Carnitine, fatty acid ester salts 544-35-4, Ethyl linoleate 544-63-8, Myristic acid, biological studies 577-11-7, Sodium docusate 616-91-1, N-Acetylcysteine 640-79-9, Glycochenodeoxycholic acid 665-66-7, Amantadine hydrochloride 737-31-5, Diatrizoate sodium 863-57-0, Sodium glycocholate 865-21-4, Vinblastin 1002-62-6, Sodium caprate 1115-70-4, Metformin hydrochloride 1264-72-8, Colistin sulfate 1309-42-8, Magnesium hydroxide 1310-58-3, Potassium hydroxide, biological studies 1310-73-2, Sodium hydroxide, biological studies 1319-82-0, Aminocaproic acid 1327-43-1, Magnesium aluminum silicate 1330-80-9, Propylene glycol monooleate 1335-30-4, Aluminum silicate 1336-21-6, Ammonium hydroxide 1338-39-2, Span 20 1338-41-6, Sorbitan monostearate 1338-43-8, Span 80 1397-89-3, Amphotericin B 1403-66-3, Gentamycin 1404-90-6, Vancomycin 1405-20-5, Polymixin B sulfate 1405-37-4, Capreomycin sulfate 1405-87-4, Bacitracin 1492-18-8, Leucovorin calcium 1501-84-4, Rimantadine hydrochloride 1684-40-8, Tacrine hydrochloride 1695-77-8, Spectinomycin 1935-18-8, Palmitoyl carnitine 2016-88-8, Amiloride hydrochloride 2364-67-2, Palmitoyl carnitine 2466-77-5, Lauroyl carnitine 2646-38-0, Sodium chenodeoxycholate 2898-95-5, Sodium ursodeoxycholate 3056-17-5, Stavudine 3485-62-9, Clidinium bromide 3778-73-2, Isofosfamide 3858-83-1, P-Aminobenzamidine 4291-63-8, Cladribine 5534-95-2, Pentagastrin 6303-21-5D, Phosphinic acid, **dipeptide** derivs. 6493-05-6, Pentoxifylline 7087-68-5, Diisopropylethylamine 7481-89-2, Zalcitabine 7585-39-9D, β-Cyclodextrin, ethers with propanediol 7647-01-0, Hydrochloric acid, biological studies 7648-98-8, Ambenonium 7664-38-2, Phosphoric acid, biological studies 7664-93-9, Sulfuric acid, biological studies 7664-93-9D, Sulfuric acid, alkyl esters, salts, biological studies 7697-37-2, Nitric acid, biological studies 8007-43-0, Sorbitan sesquioleate 8068-28-8, Colistimethate sodium 9001-28-9, Factor IX

9002-01-1, Streptokinase 9002-60-2, Corticotropin, biological studies 9002-92-0, Brij 35 9002-96-4 9003-01-4D, Polyacrylic acid, conjugates with bacitracin 9003-39-8D, Polyvinylpyrrolidone, reaction products with phosphatidylethanolamine 9004-10-8, Insulin, biological studies 9004-17-5, Insulin protamine zinc 9004-32-4D, Carboxymethyl cellulose, conjugates with pepstatin 9004-34-6, Cellulose, biological studies 9004-34-6D, Cellulose, ethers, biological studies 9004-38-0, Cellulose acetate phthalate 9004-57-3, Ethyl cellulose 9004-81-3 9004-95-9, **Polyethylene glycol** cetyl ether 9004-96-0, Crodet O40 9004-98-2, Polyoxyethylene oleyl ether 9004-99-3 9005-00-9, Polyoxyethylene stearyl ether 9005-02-1, Kessco **PEG** 300DL 9005-07-6, Kessco **PEG** 1540DO 9005-08-7 9005-32-7, Alginic acid 9005-63-4D, fatty acid esters 9005-64-5, Tween 20 9005-65-6, Polysorbate 80 9005-66-7, Tween 40 9005-67-8, Tween 60 9007-48-1, Plurol Oleique 9007-92-5, Glucagon, biological studies 9011-21-6 9012-76-4, Chitosan 9012-76-4D, Chitosan, conjugates with antipain and EDTA 9015-68-3, Asparaginase 9034-40-6, Gonadotropin releasing hormone 9035-81-8, Trypsin inhibitor 9036-19-5 9039-53-6, Urokinase 9041-93-4, Bleomycin sulfate 9050-31-1, Hydroxypropylmethyl cellulose phthalate 9062-90-2 9063-46-1 9076-44-2, Chymostatin 9078-38-0, Soybean trypsin inhibitor 9087-70-1, Pancreatic trypsin inhibitor 10034-85-2, Hydriodic acid 10035-10-6, Hydrobromic acid, biological studies 10041-19-7D, derivs. 10043-35-3, Boric acid, biological studies 10596-23-3 11000-17-2, Vasopressin 11061-68-0, Human insulin 11140-04-8, Imwitor 988 12584-58-6, Porcine insulin 12629-01-5, Human growth hormone 13265-10-6, Methscopolamine 13284-86-1, Sodium lithocholate 13780-71-7D, Boronic acid, α-aminoalkyl derivs. 14440-80-3, Stearoyl-2-lactylate 14605-22-2, Tauroursodeoxycholic acid 15500-66-0, Pancuronium bromide 15663-27-1, Cisplatin 15686-71-2, Cephalexin 15826-37-6, Cromolyn sodium 16679-58-6, Desmopressin 16960-16-0, Cosyntropin 17438-29-8 18323-44-9, Clindamycin 18883-66-4, Streptozocin 20537-88-6, Amifostine
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compns. for enhanced absorption of hydrophilic drugs using combination of surfactants)

IT 21215-62-3, Calcitonin human 21645-51-2, Aluminum hydroxide, biological studies 21679-14-1, Fludarabine 22254-24-6, Ipratropium bromide 22882-95-7, Isopropyl linoleate 23031-32-5, Terbutaline sulfate 23214-92-8, Doxorubicin 24356-60-3, Cephapirin sodium 24938-16-7, Eudragit E 25126-32-3, Sincalide 25168-73-4, Sucrose monostearate 25212-88-8, Eudragit L100-55 **25322-68-3**, **Polyethylene glycol** 25339-99-5, Sucrose monolaurate 25496-72-4, Monoolein 25597-07-3, Myristoylcarnitine 25637-84-7, Glyceryl dioleate 25637-97-2, Sucrose dipalmitate 26264-14-2D, Propanediol, ethers with β-cyclodextrin 26266-57-9, Sorbitan monopalmitate 26266-58-0, Sorbitan trioleate 26402-22-2, Glyceryl monocaprate 26402-26-6, Glyceryl monocaprylate 26446-38-8, Sucrose monopalmitate 26589-39-9, Eudragit S 26658-19-5, Sorbitan tristearate 26839-75-8, Timolol 27164-46-1, Cefazolin sodium 27195-16-0, Sucrose distearate 27214-38-6, Nikkol MGM 27215-38-9, Imwitor 312 27638-00-2, Glyceryl dilaurate 29122-68-7, Atenolol 30516-87-1, Zidovudine 31694-55-0D, C8-10-esters 33434-24-1, Eudragit RL 33515-09-2, Gonadorelin 33564-30-6, Cefoxitin sodium 34787-01-4, Ticarcillin 36354-80-0, Glyceryl dicaprylate 36791-04-5, Ribavirin 37220-82-9, Peceol 37321-62-3, Lauroglycol 37330-34-0, Bowman-Birk inhibitor 37330-34-0D, Bowman-Birk inhibitor, conjugates with polyacrylic acid 37691-11-5, Antipain 37691-11-5D, Antipain, conjugates with chitosan and EDTA 38916-34-6, Somatostatin 39324-30-6, Pepstatin 39324-30-6D, Pepstatin, conjugates with CM-cellulose 39366-43-3, Magnesium aluminum hydroxide 39438-11-4, Sorbitan monocaprate 41575-94-4, Carboplatin 42057-22-7,

Mezlocillin sodium 42540-40-9, Cefamandole nafate 42766-91-6, Nikkol DHC 42907-92-6, Sodium tauro-24,25-dihydrofusidate 47931-85-1, Calcitonin salmon 50700-72-6, Vecuronium bromide 51192-09-7, Tagat O2 51384-51-1, Metoprolol 51822-44-7, Eudragit L 51938-44-4, Sorbitan sesquistearate 52504-24-2, Softigen 767 52581-71-2, Volpo 3 52907-01-4, Cellulose acetate trimellitate 53168-42-6, Myvacet 9-45 53237-50-6 53910-25-1, Pentostatin 53988-07-1, Glyceryl dicaprate 54063-53-5, Propafenone 54392-26-6, Sorbitan monoisostearate 54910-89-3, Fluoxetine 55123-66-5, Leupeptin 56180-94-0, Acarbose 57107-95-6 57171-56-9 57248-88-1, Pamidronate disodium 58561-47-0, Softigen 701 58970-76-6, Bestatin 59227-89-3, 1-Dodecylazacycloheptan-2-one 59703-84-3, Piperacillin sodium 59721-29-8, Camostat mesylate 60177-36-8, Sorbitan monocaprylate 61270-78-8, Cefonicid sodium 61489-71-2, Menotropin 61869-08-7, Paroxetine 62013-04-1, Dirithromycin 62288-83-9, Desmopressin acetate 62893-19-0, Cefoperazone 63527-52-6, Cefotaxime 64228-81-5, Atracurium besylate 64480-66-6, Glycoursodeoxycholic acid 64544-07-6, Cefuroxime axetil 66376-36-1, Alendronate 66419-50-9, Bovine growth hormone 67352-02-7 67655-94-1, Amastatin 68099-86-5, Bepridil hydrochloride 68401-81-0, Ceftizoxime 68795-69-7, Propylene glycol monocaprate 68958-64-5 69049-74-7, Nedocromil sodium 69070-98-0 69227-93-6, Lauryl β-maltopyranoside 69655-05-6, Didanosine 70458-92-3, Pefloxacin 70458-96-7, Norfloxacin 71486-22-1, Vinorelbine 73384-59-5, Ceftriaxone 74011-58-8, Enoxacin 74356-00-6, Cefotetan disodium 74381-53-6, Leuprolide acetate 76420-72-9, Enalaprilat 76470-66-1, Loracarbef 78110-38-0, Aztreonam 79350-37-1, Cefixime 79517-01-4, Octreotide acetate 79665-92-2 79665-93-3 81161-17-3, Esmolol hydrochloride 82410-32-0, Ganciclovir 82419-36-1, Ofloxacin 83869-56-1, Granulocyte-macrophage colony stimulating factor 83905-01-5, Azithromycin 85721-33-1, Ciprofloxacin 87679-37-6, Trandolapril 88669-04-9, Trospectomycin 89703-10-6, FK-448 89987-06-4, Tiludronate 93790-70-6, Cholylsarcosine 93790-72-8, N-Methyltaurocholic acid 93792-59-7, Hydroxypropylmethyl cellulose succinate 94749-08-3, Salmeterol xinafoate 98036-77-2, Hydrotalcite 98079-51-7, Lomefloxacin 100986-85-4, Levofloxacin 104227-87-4, Famciclovir 105287-09-0, Aquateric 105462-24-6, Risedronic acid 106392-12-5, Polyoxyethylene-polyoxypropylene block copolymer 106819-53-8, Doxacurium chloride 106861-44-3, Mivacurium chloride 107648-80-6, Cefepime hydrochloride 110871-86-8, Sparfloxacin 113189-02-9, Antihemophilic factor 113852-37-2, Cidofovir 116094-23-6, Insulin aspart 119914-60-2, Grepafloxacin 121368-58-9, Olpadronate 121548-04-7, Gelucire 44/14 121548-05-8, Gelucire 50/13 124832-26-4, Valaciclovir 126467-48-9, Porcine somatotropin 127759-89-1, Lobucavir 127829-97-4, Solulan C 24 133107-64-9, Insulin lispro 134678-17-4, Lamivudine 137862-53-4, Valsartan 138636-14-3, Eudragit NE 139110-80-8, Zanamivir 139639-23-9, Tissue type plasminogen activator 142368-40-9, Imwitor 375 143003-46-7, Alglucerase 143011-72-7, Granulocyte colony stimulating factor 146961-76-4, Alatrofloxacin 147059-72-1, Trovafloxacin 148046-81-5, Gelucire 33/01 148553-50-8, Pregabalin 150372-93-3, Glycerox L 151126-32-8, Pramlintide 154361-50-9, Capecitabine 156259-68-6, Capmul MCM 157810-81-6, Indinavir sulfate 160337-95-1, Insulin glargine 169148-63-4, Insulin detemir 173146-27-5, Denileukin diftitox 191588-94-0, TNK-tPA 679809-58-6, Enoxaparin sodium
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compns. for enhanced absorption of hydrophilic drugs using combination of surfactants)

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L28 ANSWER 11 OF 16 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2000:697801 CAPLUS
DOCUMENT NUMBER: 134:136596
TITLE: Synthesis and HPLC analysis of enzymatically cleavable linker consisting of poly(ethylene glycol) and dipeptide for the development of immunoconjugate
AUTHOR(S): Suzawa, T.; Nagamura, S.; Saito, H.; Ohta, S.; Hanai, N.; Yamasaki, M.
CORPORATE SOURCE: Tokyo Research Laboratories, Kyowa Hakko Kogyo Co., Ltd., Asahi-machi, Machida-shi, Tokyo, 194-8533, Japan
SOURCE: Journal of Controlled Release (2000), 69(1), 27-41
CODEN: JCREEC; ISSN: 0168-3659
PUBLISHER: Elsevier Science Ireland Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A model compound of antitumor agent, segment B of duocarmycin **deriv** . DU-86, was conjugated to tumor-specific antibody via a cleavable linker consisting of poly(ethylene glycol) (PEG) and dipeptide, l-alanyl-l-valine (Ala-Val), to confirm the feasibility of the linker for application to immunoconjugate. The release of segment B from the linker was evaluated by HPLC anal. When segment B was **derivatized** to have an amino residue and then linked to PEG through a dipeptide, segment B was cleaved at the peptide bond by a particular enzyme, thermolysin (EC 3.4.24.4), but not by plasmin (EC 3.4.2 1.7), indicating that certain protease specifically expressed at the tumor site would be capable of peptide-specific digestion and release of anti-tumor agent since a thermolysin-like enzyme has been reported to be expressed at many tumor cells. Furthermore, the results showing that cell extract from G361 human melanoma had an ability to digest the linker peptide while the linker was stable in normal human serum suggested the tumor-specific activation of the conjugated agent. Segment B was conjugated via the linker to murine monoclonal antibody KM641 reactive to GD3 ganglioside to form immunoconjugate and the quant. release of segment B under the treatment with the enzyme was also confirmed. These results indicate the possibility of double targeting based on both the recognition ability of tumor specific antibody and tumor specific activation of the antitumor agents to enhance tumor treatment efficacy and to decrease unwanted side effects.

CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1, 15

ST duocarmycin segment **dipeptide polyethylene glycol** immunoconjugate; enzyme duocarmycin segment release immunoconjugate antitumor

IT Drug delivery systems
(immunoconjugates; synthesis and HPLC anal. of enzymically cleavable linker consisting of **PEG** and **dipeptide** for development of immunoconjugate)

IT Antitumor agents
(melanoma; synthesis and HPLC anal. of enzymically cleavable linker consisting of **PEG** and **dipeptide** for development of immunoconjugate)

IT Antibodies
RL: ANT (Analyte); SPN (Synthetic preparation); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); PREP (Preparation); USES (Uses)
(monoclonal, **conjugates**; synthesis and HPLC anal. of enzymically cleavable linker consisting of **PEG** and **dipeptide** for development of immunoconjugate)

IT Antitumor agents
Drug targeting
(synthesis and HPLC anal. of enzymically cleavable linker consisting of

PEG and **dipeptide** for development of immunoconjugate)
IT 62010-37-1, Ganglioside GD3
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(antibody to; synthesis and HPLC anal. of enzymically cleavable linker consisting of **PEG** and **dipeptide** for development of immunoconjugate)
IT 321862-60-6P 321862-62-8P
RL: ANT (Analyte); RCT (Reactant); SPN (Synthetic preparation); ANST (Analytical study); PREP (Preparation); RACT (Reactant or reagent)
(synthesis and HPLC anal. of enzymically cleavable linker consisting of **PEG** and **dipeptide** for development of immunoconjugate)
IT 321862-60-6DP, **conjugates** with monoclonal antibodies
RL: ANT (Analyte); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(synthesis and HPLC anal. of enzymically cleavable linker consisting of **PEG** and **dipeptide** for development of immunoconjugate)
IT 9001-90-5, Plasmin 9068-59-1
RL: CAT (Catalyst use); USES (Uses)
(synthesis and HPLC anal. of enzymically cleavable linker consisting of **PEG** and **dipeptide** for development of immunoconjugate)
IT 100-39-0, Benzyl bromide 134-96-3, 4-Hydroxy-3,5-dimethoxybenzaldehyde 501-53-1, Benzyloxycarbonyl chloride 1149-26-4, Benzyloxycarbonyl-L-valine 1816-92-8, Methyl azidoacetate 2576-47-8, 2-Bromoethylamine hydrobromide 3401-36-3 13518-40-6, L-Valine-tert-butyl ester hydrochloride 39927-08-7 53089-97-7
RL: RCT (Reactant); RACT (Reactant or reagent)
(synthesis and HPLC anal. of enzymically cleavable linker consisting of **PEG** and **dipeptide** for development of immunoconjugate)
IT 6527-32-8P 53844-02-3P 185218-55-7P 185218-57-9P 185218-58-0P 185218-71-7P 185218-72-8P 303738-94-5P 303738-98-9P 321862-61-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(synthesis and HPLC anal. of enzymically cleavable linker consisting of **PEG** and **dipeptide** for development of immunoconjugate)
REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L28 ANSWER 12 OF 16 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:240985 CAPLUS
DOCUMENT NUMBER: 132:292701
TITLE: Novel methods for therapeutic vaccination
INVENTOR(S): Steinaa, Lucilla; Mouritsen, Soren; Nielsen, Klaus Gregorious; Haaning, Jesper; Leach, Dana; Dalum, Iben; Gautam, Anand; Birk, Peter; Karlsson, Gunilla
PATENT ASSIGNEE(S): M & E Biotech A/S, Den.
SOURCE: PCT Int. Appl., 220 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000020027	A2	20000413	WO 1999-DK525	19991005
WO 2000020027	A3	20001012		

W: AE, AL, AM, AT, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, CZ, DE, DE, DK, DK, DM, EE, EE, ES, FI, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK,

LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

CA 2345817	AA	20000413	CA 1999-2345817	19991005	
AU 9958510	A1	20000426	AU 1999-58510	19991005	
AU 751709	B2	20020822			
EP 1117421	A2	20010725	EP 1999-945967	19991005	
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, MC, IE, SI, LT, LV, FI, RO					
JP 2002526419	T2	20020820	JP 2000-573386	19991005	
EE 200100203	A	20021015	EE 2001-203	19991005	
NZ 511055	A	20031031	NZ 1999-511055	19991005	
NO 2001001586	A	20010531	NO 2001-1586	20010328	
ZA 2001002603	A	20020930	ZA 2001-2603	20010329	
HR 2001000319	A1	20020630	HR 2001-319	20010504	

PRIORITY APPLN. INFO.:	DK 1998-1261	A	19981005
	US 1998-105011P	P	19981020
	WO 1999-DK525	W	19991005

AB A method is disclosed for inducing cell-mediated immunity against cellular antigens. More specifically, the invention provides for a method for inducing cytotoxic T-lymphocyte immunity against weak antigens, notably self-proteins. The method entails that antigen presenting cells are induced to present at least one CTL epitope of the weak antigen and at the same time presenting at least one foreign T-helper lymphocyte epitope. In a preferred embodiment, the antigen is a cancer specific antigen, e.g. prostate specific membrane antigen (PSM), Her2, or FGF8b. The method can be exercised by using traditional polypeptide vaccination, but also by using live attenuated vaccines or nucleic acid vaccination. The invention furthermore provides immunogenic analogs of PSM, Her2 and FGF8b, as well as nucleic acid mols. encoding these analogs. Also vectors and transformed cells are disclosed. The invention also provides for a method for identification of immunogenic analogs of weak or non-immunogenic antigens.

IC A61K039-00

CC 15-2 (Immunochemistry)
Section cross-reference(s): 3, 63

IT **Interferons**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(γ; weak antigens inserted with foreign T cell epitope as vaccines)

IT 99-20-7D, Trehalose, diester 7429-90-5, Aluminum, biological studies 9004-54-0, Dextran, biological studies 9005-25-8, Starch, biological studies **25322-68-3** 53678-77-6, Muramyl **dipeptide**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(adjuvant; weak antigens inserted with foreign T cell epitope as vaccines)

L28 ANSWER 13 OF 16 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER:	1997:44674 CAPLUS
DOCUMENT NUMBER:	126:65386
TITLE:	Preparation of antitumor toxin complexes
INVENTOR(S):	Suzawa, Toshiyuki; Yamasaki, Motoo; Nagamura, Satoru; Saito, Hiromitsu; Ohta, So; Hanai, Nobuo
PATENT ASSIGNEE(S):	Kyowa Hakko Kogyo Co., Ltd., Japan
SOURCE:	PCT Int. Appl., 78 pp. CODEN: PIXXD2
DOCUMENT TYPE:	Patent

LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9635451	A1	19961114	WO 1996-JP1241	19960510
W: CA, JP, US				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2220339	AA	19961114	CA 1996-2220339	19960510
EP 867190	A1	19980930	EP 1996-913722	19960510
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
US 6103236	A	20000815	US 1997-981416	19971110
US 6638509	B1	20031028	US 2000-500243	20000208

PRIORITY APPLN. INFO.: JP 1995-111933 A 19950510
WO 1996-JP1241 W 19960510
US 1997-981416 A3 19971110

AB A toxin complex is prepared by bonding a residue of a compound having target cell affinity and a residue of toxin via a spacer containing a polyalkylene glycol and a dipeptide. The compds. which show cell affinity include tumor-specific antibody and its fragments. For example, HO-PEG-Ala-Val-adriamycin reaction products with NL-1 (acute lymphocytic leukemia antibody) was prepared and its antiproliferative effect against Daudi Burkitt's lymphoma cells was tested.

IC ICM A61K039-44
ICS C07K017-06

CC 63-5 (Pharmaceuticals)
Section cross-reference(s): 1

ST antitumor antibody spacer complex prepn; adriamycin antibody **PEG** **dipeptide** complex prepn

IT 20830-81-3DP, Daunorubicin, reaction products with **PEG** -Ala-Val-OH **derivative** and antibody 25316-40-9DP, Adriamycin, reaction products with **PEG**-Ala-Val-OH **derivative** and antibody 185218-46-6DP, reaction products with adriamycin and antibody 185218-48-8DP, reaction products with adriamycin and antibody 185218-50-2DP, reaction products with adriamycin and antibody 185218-52-4DP, reaction products with **PEG**-Ala-Val-OH **derivative** and antibody 185218-65-9DP, reaction products with **PEG**-Ala-Val-OH **derivative** and antibody 185218-74-0DP, reaction products with KM-641 antibody
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of antitumor toxin complex via spacer containing polyalkylene glycol and **dipeptide**)

IT 100-02-7, 1-Hydroxy-4-nitrobenzene, reactions 100-39-0, Benzyl bromide 106-93-4, 1,2-Dibromoethane 107-09-5, 2-Bromoethylamine 109-64-8, 1,3-Dibromopropane 134-96-3, 4-Hydroxy-3,5-dimethoxybenzaldehyde 501-53-1, Benzyloxycarbonyl chloride 537-73-5 2812-46-6 2899-60-7 3401-36-3 6959-47-3, Picolyl chloride hydrochloride 13518-40-6 **25322-68-3** 146940-68-3
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of antitumor toxin complex via spacer containing polyalkylene glycol and **dipeptide**)

IT 6527-32-8P 16980-82-8P 26403-74-7P, **Polyethylene** **glycol** monobenzyl ether 29375-30-2P 53089-97-7P 53844-02-3P 60166-68-9P 62054-92-6P 185218-31-9P 185218-34-2P 185218-38-6P 185218-42-2P 185218-44-4P 185218-52-4P 185218-55-7P 185218-57-9P 185218-58-0P 185218-59-1P 185218-60-4P 185218-61-5P 185218-62-6P

185218-64-8P 185218-65-9P 185218-66-0P 185218-67-1P 185218-68-2P
185218-69-3P 185218-70-6P 185218-71-7P 185218-72-8P 185218-73-9P
185218-74-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of antitumor toxin complex via spacer containing polyalkylene glycol and **dipeptide**)

L28 ANSWER 14 OF 16 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1992:610735 CAPLUS
DOCUMENT NUMBER: 117:210735
TITLE: Enzymic manufacture of physiologically active dipeptides
INVENTOR(S): Ri, Hiroki; Fukushi, Hideaki
PATENT ASSIGNEE(S): Chisso Corp., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 5 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 04187095	A2	19920703	JP 1990-315821	19901122

PRIORITY APPLN. INFO.: JP 1990-315821 19901122

AB Dipeptides useful as analgesics or flavoring agents are manufactured in a solvent with cysteine proteinase that can be used as its natural form, immobilized form, or **derivs.** modified with a high mol. weight substance, e.g. PEG. Manufacture of benzyloxycarbonyltyrosylarginine with papain **derivatized** with methoxypolyethyleneglycol succinic acid N-succinimide was shown. The effect of the EtOH concentration in the solvent system on the yield of the product was also discussed.

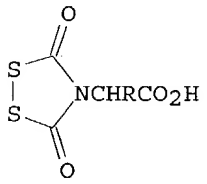
IC ICM C12P021-02
CC 16-2 (Fermentation and Bioindustrial Chemistry)
Section cross-reference(s): 17
ST **dipeptide** manuf cysteine proteinase; **PEG** modification
papain **dipeptide** manuf
IT **25322-68-3, Polyethylene glycol**
RL: BIOL (Biological study)
(cysteine-type proteinase modified with, for **dipeptide** manufacture)
IT 9001-73-4D, Papain, **PEG derivative**
RL: BIOL (Biological study)
(**dipeptide** manufacture with)
IT 64-17-5, Ethanol, uses
RL: USES (Uses)
(in **dipeptide** manufacture with **PEG-derivatized** papain, effect on product yield of)
IT 76264-10-3P 88273-37-4P
RL: BMF (Bioindustrial manufacture); BIOL (Biological study); PREP (Preparation)
(manufacture of, with PEG-**derivatized** papain)
IT 1164-16-5 26340-89-6
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, in **dipeptide** manufacture with **PEG-derivatized** papain)
IT 71-55-6, 1,1,1-Trichloroethane
RL: BIOL (Biological study)
(solvent containing, in **dipeptide** manufacture with **PEG-**

derivatized papain)

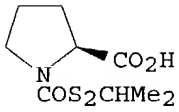
L28 ANSWER 15 OF 16 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1992:18001 CAPLUS
DOCUMENT NUMBER: 116:18001
TITLE: **Polyethylene glycol** modified trypsin kinetics in buffer and in benzene: **dipeptide** synthesis
AUTHOR(S): Munch, Olivier; Tritsch, Denis; Biellmann, Jean Francois
CORPORATE SOURCE: Dep. Chim., Univ. Louis Pasteur, Strasbourg, F-67008, Fr.
SOURCE: Biocatalysis (1991), 5(1), 35-47
CODEN: BIOCED; ISSN: 0886-4454
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Trypsin, on chemical modification with 2-[(o-monomethoxy) polyethyleneglycol]-4,6-dichloro-striazine, is soluble in benzene. In buffer, this modification increased the amidolytic and esterolytic mol. activity kcat relative to the native enzyme and decreased strongly the Michaelis constant (Km) of Nα-benzoyl-L-arginine-p-nitroanilide , while that of Nα-benzoyl-L-arginine Et ester (Bz-L Arg-OEt) did not change. The modified enzyme catalyzed the aminolysis of the anilide in benzene with trace amts. of water. Syntheses of dipeptides were enzymically performed with high yields using Nα-benzoyl-L-arginine Et ester or Nα-benzoyl-L-lysine Me ester (Bz-L-LysOMe) as acyl-group donors, and L-leucinamide (L-LeuNH2) as an acceptor nucleophile.
CC 9-14 (Biochemical Methods)
Section cross-reference(s): 7, 34
ST **polyethylene glycol** trypsin **dipeptide** synthesis; enzyme solvent peptide synthesis
IT Aminolysis catalysts
(**PEG**-modified trypsin, in **dipeptide** synthesis)
IT Aminolysis
(of arginine or lysine **derivs.**, by leucine, PEG modified trypsin catalysis of)
IT 687-51-4
RL: ANST (Analytical study)
(aminolysis by, of arginine or lysine **derivs.**, PEG-modified trypsin-catalysis of, in benzene)
IT 9002-07-7, Trypsin
RL: ANST (Analytical study)
(modification of, with **polyethylene glycol**, organic solvent-solubility and **dipeptide** synthesis in relation to)

L28 ANSWER 16 OF 16 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1989:8634 CAPLUS
DOCUMENT NUMBER: 110:8634
TITLE: A convenient general method for synthesis of Nα- or Nω-dithiasuccinoyl (Dts) amino acids and **dipeptides**: application of **polyethylene glycol** as a carrier for functional purification
AUTHOR(S): Zalipsky, Shmuel; Albericio, Fernando; Slomczynska, Urszula; Barany, George
CORPORATE SOURCE: Dep. Chem., Univ. Minnesota, Minneapolis, MN, USA
SOURCE: International Journal of Peptide & Protein Research (1987), 30(6), 740-83
CODEN: IJPPC3; ISSN: 0367-8377
DOCUMENT TYPE: Journal

LANGUAGE: English
OTHER SOURCE(S): CASREACT 110:8634
GI



I



II

No

AB Nα Dithiasuccinoyl (Dts) amino acids, e.g. I (R = H, Me, CHMe2, CH2CHMe2, CH2Ph, etc.), needed for solid-phase peptide synthesis have been prepared in good yields and excellent purities by a new method that exploits the solubility properties of polyethylene glycol (PEG; bifunctional with average mol. weight 2000 was found to be optimal). Suitably side-chain protected amino acid **derivs.** are first reacted with polymeric xanthate PEG-OCS2CH2CONH2, following which the free α-carboxyl is blocked by silylation and the Dts heterocycle is elaborated in the same pot by reaction with ClCOSCl. Upon aqueous workup, the polymeric carrier removes any urethane blocked amino acids which arise during the process. Exaggerated conditions were explored to prove the power of this functional purification approach, and mechanisms of formation of polymer-bound urethanes are proposed and supported by solution model studies. The preparation and characterization of the companion proline **derivative** II is also presented.
CC 34-3 (Amino Acids, Peptides, and Proteins)
IT 26555-35-1, Ethoxycarbonylsulfenyl chloride
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with polyethyleneglycol-bound glycine **derivative**)
IT 10416-59-8 13435-12-6, N-(Trimethylsilyl)acetamide 18148-61-3, N-(Trimethylsilyl)urea 18297-63-7, N,N'-Bis(Trimethylsilyl)urea
RL: RCT (Reactant); RACT (Reactant or reagent)
(silylation by, of polyethyleneglycol-bound amino acid **derivs**

=> fil wpids
FILE 'WPIDS' ENTERED AT 12:35:23 ON 10 MAY 2004
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FILE LAST UPDATED: 5 MAY 2004 <20040505/UP>
MOST RECENT DERWENT UPDATE: 200429 <200429/DW>
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>>> THE DISPLAY LAYOUT HAS BEEN CHANGED TO ACCOMODATE THE
    NEW FORMAT GERMAN PATENT APPLICATION AND PUBLICATION
    NUMBERS. SEE ALSO:
    http://www.stn-international.de/archive/stnews/news0104.pdf <<<

>>> SINCE THE FILE HAD NOT BEEN UPDATED BETWEEN APRIL 12-16
    THERE WAS NO WEEKLY SDI RUN  <<<

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                ETHYLENE OR POLYETHYLENE)(W) GLYCOL
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L3        42968 SEA FILE=WPIDS ABB=ON  PLU=ON  L1 OR L2
L4         6160 SEA FILE=WPIDS ABB=ON  PLU=ON  INTERFERON
L5        41386 SEA FILE=WPIDS ABB=ON  PLU=ON  CONJUGAT?
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L13        1631 SEA FILE=WPIDS ABB=ON  PLU=ON  IFN OR IFNALPHA OR IFNALPHA2A
L14          20 SEA FILE=WPIDS ABB=ON  PLU=ON  L13 (L) L3 (L) L5
L15           2 SEA FILE=WPIDS ABB=ON  PLU=ON  L14 AND L11
L16           4 SEA FILE=WPIDS ABB=ON  PLU=ON  L12 OR L15
L17           8 SEA FILE=WPIDS ABB=ON  PLU=ON  L3 AND (L4 OR L13) AND L11
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L19         378 SEA FILE=WPIDS ABB=ON  PLU=ON  POLYMER? (S) (L4 OR L13)
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L21           6 SEA FILE=WPIDS ABB=ON  PLU=ON  L20 AND L5
L22          12 SEA FILE=WPIDS ABB=ON  PLU=ON  L21 OR L18


=> d .wp l22 1-12

L22  ANSWER 1 OF 12  WPIDS  COPYRIGHT 2004 THOMSON DERWENT on STN
AN   2004-248326 [23]    WPIDS
DNN  N2004-197022        DNC C2004-097055
TI   Novel inhibitor deactivatable by reagent produced by target cell, having
     first moiety that inhibits, suppresses, neutralizes or decreases activity
     of biologically active agent, operably linked to second moiety cleavable
     by reagent.
DC   B04 B05 D16 P31
IN   LAUERMANN, V
PA   (LAUE-I) LAUERMANN V
CYC  104
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PI WO 2004021861 A2 20040318 (200423)* EN 35
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
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ADT WO 2004021861 A2 WO 2003-US27372 20030830
PRAI US 2003-407471 20030830; US 2002-407471P 20020903
AB WO2004021861 A UPAB: 20040405
NOVELTY - An inhibitor which is deactivatable by reagent produced by target cell, having first moiety that binds, inhibits, suppresses, neutralizes or decreases activity of biologically active agent, that is operably linked to second moiety cleavable by reagent produced by target cell, and where specific cleavage of second moiety causes reduction of binding, inhibiting, suppressing or neutralizing activity of inhibitor, is new.

DETAILED DESCRIPTION - An inhibitor (I) which is deactivatable by a reagent produced by a target cell, comprising a first moiety that binds, inhibits, suppresses, neutralizes or decreases activity of a biologically active agent, where the first moiety is operably linked to, a second moiety specifically cleavable by a reagent produced by a target cell, where the first and second moieties are not attached in nature and where specific cleavage of the second moiety causes reduction of binding, inhibiting, suppressing or neutralizing activity of the inhibitor.

ACTIVITY - Cytostatic.

Ten nude mice (8 weeks old) were injected subcutaneously with 5 million A431 cells or A431 cells secreting active prostate specific antigen (PSA) (A431/PSA), and 10 mice were used as controls. Animals were also given intraperitoneal injections of 500 mu g of anti-epidermal growth factor receptor (EGFR) antibody or antibody/inhibitor complex, injections for every 3 days for 28 days. Tumors were measured twice a week and volume was calculated. After 30 days, antibody treated A431 group displayed a reduced tumor growth when compared to group treated with irrelevant antibody. Antibody/inhibitor complex treated A431 group displayed slightly reduced tumor growth when compared to group treated with irrelevant antibody. Antibody treated with A431/PSA displayed reduced tumor growth. Similar effect was also seen with A431 group. About 300 mu g of antibody/inhibitor complex was needed in A431/PSA group to achieve similar tumor growth inhibition as in A431/PSA group treated with 500 mu g of anti-EGFR antibody. Results showed that after two months, all control animals developed significant tumors, 50% of the animals treated with antibody developed significant tumor mass and only 30% of the animals treated with antibody/inhibitor complex developed significant tumors.

MECHANISM OF ACTION - Inhibitor of cancer growth (claimed).

USE - (I) is useful for site specific activation of an active agent which involves administering (I), and restoring activity of the active agent, where the inhibitor is administered alone or together with an active agent such that the activity of the active agent is reduced until it reaches a target cell producing a reagent, where the inhibitor is cleaved by the reagent and activity of the active agent is restored. The administration to the vertebrate has a desired treatment effect. (I) is also useful for treating a cancer cell which involves contacting the cell with (I), and restoring activity of the active agent, where the inhibitor is administered alone or together with an active agent such that the activity of the active agent is reduced until it reaches a target cell producing a reagent, where the inhibitor is cleaved by the reagent and activity of the active agent is restored. The inhibitor is administered in a composition comprising the inhibitor alone or together with an active

agent and a carrier, diluent or excipient to a vertebrate. The cancer is colon cancer, prostate cancer, breast cancer, T cell or B cell lymphoproliferative disease, cancer cell expressing a plasma membrane tyrosine kinase receptor, head and neck caner, squamous cell cancer, gastrointestinal cancer, non-small cell lung cancer, melanoma, kidney cancer, ovarian cancer or pancreatic cancer cell (all claimed). Dwg.0/0

TECH UPTX: 20040405

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Inhibitor: In (I), the first moiety is chosen from a peptide, cyclic peptide, polypeptide, peptidomimetic, protein, fusion protein, hybrid molecule or a dimer, multimer, a naturally occurring inhibitor, soluble receptor, an antibody, a monoclonal antibody, bispecific antibody, antibody fragment, single chain antibody, peptabody, a peptide, a cyclic peptide, a peptide-lipid **conjugate**, hormone, antigen, epitope, receptor, chemokine, nucleic acid or a dimer, multimer, or a **conjugate** of the above. (I) is chosen from antibody inhibitor, monoclonal antibody inhibitor, bispecific antibody inhibitor, catalytic antibody inhibitor, peptabody inhibitor, receptor inhibitor, soluble receptor inhibitor, a hormone inhibitor, a peptide inhibitor, cyclic peptide inhibitor, peptide lipid **conjugate** inhibitor, peptide nucleic acid **conjugate** inhibitor, nucleic acid/protein **conjugate** inhibitor, a delivery-enhancing transporter inhibitor, pepducin inhibitor, cytokine inhibitor, chemokine inhibitor, circularly permuted chemokine inhibitor, an interleukin inhibitor, **interferon** inhibitor, or a dimer or multimer of the above. The active agent is chosen from an antibody, monoclonal antibody, bispecific antibody, antibody fragment, single chain antibody, peptabody, diabody, triabody, peptide, pepducin, a cyclic peptide, a peptide-lipid **conjugate**, a cell penetrating moiety, a membrane-tethering moiety, a nucleic acid, a hormone, antigen, epitope, receptor, chemokine, cytokine, circularly permuted chemokine, circularly permuted cytokine, interleukin, **interferon**, chemical drug, a component of a biological activation cascade, coagulation system, fibrinolysis system, complement system, kinin system, an enzyme which converts the inactive precursor of a pharmacological substance into the pharmacologically active substance, a pharmacologically active substance, a coagulation factor such as thrombin, factor Va, factor VIIa, factor IXa, factor Xa, TF coagulation-active fragments and factor XIIa, thrombin which is mutated in the region of the Arg-Thr cleavage site at amino acid position 327/328, etc. In (I), at least one second moiety is embedded within the first moiety. The first and the second moieties are connected by a peptide, a lipid, nucleic acid, carbohydrate, synthetic oligosaccharide analog, synthetic glycopeptide analog, or a chemical linker. The second moiety is chosen from peptide, polypeptide, lipid, carbohydrate, polysaccharide, glycolipid, nucleic acid, or a **conjugate** of the above. The second moiety is a peptide which comprises a sequence cleavable by a protease. The second moiety is chosen from Ser-Lys-Gly-Ser-Phe-Ser-Ile-Gln-Tyr-Thr-Tyr-His-Val, His-Leu-Gly-Gly-Ser-Gln-Gln-Leu-Leu-His-Asn-Lys-**Gln**, Ser-Lys-**Gly**-Lys-Gly-Thr-Ser-Ser-Gln-Tyr-Ser-Asn-Thr-Glu, Asp-Arg-Val-Tyr-Ile-His-Pro-Phe, Val-Val-Cys-Gly-Glu-Arg-Gly-Phe-Phe-Tyr-Thr-Pro, Phe-Phe-Tyr-Thr-Pro-Lys-Ala, Lys-Arg-Arg-Pro-Val-Lys-Val-Tyr-Pro, Pro-Val-Gly-Lys-Lys-Arg-Arg-Pro-Val-Lys-Val-Tyr, Lys-Pro-Val-Gly-Lys-Lys-Arg-Arg-Pro-Val-Lys-Val, Gly-Lys-Pro-Val-Gly-Lys-Lys-Arg-Arg-Pro-Val-Lys, etc. In (I), the reagent is chosen from protease, lipase, nuclease, glycolytic enzyme, or prostate specific antigen, a human prostate-associated protease, matrix metalloproteinase, plasminogen activator, cathepsin, urokinase, neutrophil elastase, calpain, urokinase-type plasminogen activator, a tissue-type plasminogen activator, kallikrein, viral protease, fungal protease, bacterial protease, parasitic

protease, protease secreted by a cancer cell, a matriptase, Kunitz-type serine protease, thiol-dependent protease, Plasmodium falciparum protease, Candida acid protease, a human cytomegalovirus protease, human herpes virus protease, a varicella zoster virus protease, hepatitis A virus protease, hepatitis C virus protease, Epstein Barr virus specific protease, infectious laryngotracheitis virus protease, catalytic RNA or a catalytic antibody. The reagent is produced by endothelial cells, cells adjoining activated endothelial cells, activated or proliferating endothelial cells, tumor cells, muscle cells, smooth muscle cells, fibroblasts, macrophages, lymphocytes, liver cells, kidney cells, synovial cells, joint cells, inflammatory cells, virus-infected cells, bacteria-infected cells, parasite-infected cells, bronchial epithelial cells, glia cells or leukemia cells. The inhibitor alone or together with an active agent is in a biodegradable, biocompatible **polymeric** delivery material, in a slow release implant, in a microencapsulated composition, or **conjugate** with a biodegradable **polymer** . (I) further comprises or associates with a recognition domain that binds to a target structure, an exterior surface of a targeted cell, cell surface marker, extracellular matrix, or their components. The recognition domain binds to activated or proliferating activated endothelial cells, to tumor cells, muscle cells, smooth muscle cells, fibroblasts, macrophages, lymphocytes, liver cells, kidney cells, synovial cells, joint cells, blood vessels, inflammatory cells, virus-infected cells, bronchial epithelial cells, glia cells or leukemia cells.

L22 ANSWER 2 OF 12 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2004-214262 [20] WPIDS
CR 2004-214264 [20]
DNC C2004-084758
TI Method of treating condition associated with abnormal mammalian cell proliferation e.g. cancer, benign tumor and infectious disease involves administering isoleucine derivatives, especially isoleucine boroproline.
DC B05
IN ADAMS, S; JESSON, M I; JONES, B; MILLER, G T
PA (POIN-N) POINT THERAPEUTICS INC
CYC 105
PI WO 2004004658 A2 20040115 (200420)* EN 152
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG UZ VC VN YU ZA ZW
US 2004077601 A1 20040422 (200428)
ADT WO 2004004658 A2 WO 2003-US21405 20030709; US 2004077601 A1 Provisional US 2002-394856P 20020709, Provisional US 2002-414978P 20021001, Provisional US 2003-466435P 20030428, US 2003-616694 20030709
PRAI US 2003-466435P 20030428; US 2002-394856P 20020709;
US 2002-414978P 20021001; US 2003-616694 20030709
AB WO2004004658 A UPAB: 20040429
NOVELTY - Method (M1) of treating a condition associated with abnormal mammalian cell proliferation, involves administering isoleucine derivatives (I) by injection or in an enterically coated form
DETAILED DESCRIPTION - Method (M1) of treating a condition associated with abnormal mammalian cell proliferation, involves administering isoleucine derivatives of formula Am-NH-CH(CH(CH3)-CH2-CH3)-C(=O)-A1-R (I) (disclosed) by injection or in an enterically coated form.
A and A1 = L or D amino acids;
m = 0-10;

R = organo borates, organo phosphonates, fluoroalkylketones, alphaketos, N-peptiolyl-O-(acylhydroxylamine), azapeptide, azetidine, fluoroolefin **dipeptide** isoester, peptidyl (alpha -aminoalkyl) phosphonate ester, aminoacyl pyrrolidine-2-nitrile or 4-cyano-thiazolidide.

INDEPENDENT CLAIMS are included for following:

(1) treating (M2) an infectious disease involving administering (I) by injection or in an enterically coated form;

(2) a pharmaceutical preparation (P1) comprising (I) (0.005 - less than 1 mg/kg/day) and a carrier;

(3) a kit (K1) comprising a housing and (P1);

(4) a pharmaceutical preparation (P2) comprising (I) (less than 1 mg/kg/day). (P2) Is provided in a vial or ampoule with a septum;

(5) a kit (K2) comprising a housing containing (I) in a first container and a carrier in a second container. (I) Is in dried form;

(6) a kit (K3) comprising housing containing (I) dissolved in acid solution in a first container and a neutral or basic isotonic diluent in a second container;

(7) a kit (K4) comprising (I) in a first container and instructions for diluting (I) in neutral or acidic injectable diluent;

(8) a composition (C1) comprising (I) and antibody or its fragment;

(9) stimulating (M3) an immune response involving administering (I) and an antigen by injection or in an enterically coated form;

(10) stimulating (M4) an immune response in an immunocompromised subject involving administration of (I) to induce interleukin (IL)-1;

(11) treating (M5) a subject having or a risk of developing an **interferon** (**IFN**)-responsive condition involving administering (I);

(12) treating (M6) a subject having a risk of developing cancer involving administering (I) and an enzyme inhibitor selected from tyrosine kinase inhibitor, CDK inhibitor, mitogen activated protein (MAP) kinase inhibitor and epidermal growth factor receptor (EGFR) inhibitor; and

(13) a composition (C2) comprising (I) and a cancer antigen or microbial antigen.

ACTIVITY - Cytostatic; Antidiabetic; Antimicrobial; Antibacterial; Antitubercular; Tuberculostatic; Virucide; Anti-HIV; Fungicide; Antiparasitic; Antiinflammatory; Hepatotropic; Neuroprotective.

Mice were inoculated subcutaneously with WEHI 164 tumor cells and administered isoleucine-boroproline (a) (2 micro g) twice daily from 2-9 days after tumor inoculation. Control mice received saline. It was observed that in mice receiving (a), the tumor size was smaller as compared to that in control treated mice.

MECHANISM OF ACTION - Abnormal angiogenesis inhibitor; An antigen-specific immune response (e.g. innate immune response or an adaptive immune response) stimulator.

USE - For the treatment of a condition associated with abnormal mammalian cell proliferation, e.g. cancer (including basal cell carcinoma, biliary tract cancer, bladder cancer, bone cancer, brain cancer, breast cancer, cervical cancer, choriocarcinoma, CNS cancer, colon and rectum cancer, connective tissue cancer, cancer of the digestive system, endometrial cancer, esophageal cancer, eye cancer, cancer of the head and neck, gastric cancer, intra-epithelial neoplasm, kidney cancer, larynx cancer, leukemia, acute myeloid leukemia, acute lymphoid leukemia, chronic myeloid leukemia, chronic lymphoid leukemia, liver cancer, small cell lung cancer, non-small cell lung cancer, lymphoma, Hodgkin's or non-Hodgkin's lymphoma, melanoma, myeloma, neuroblastoma, oral cavity cancer, ovarian cancer, pancreatic cancer, prostate cancer, retinoblastoma, rhabdomyosarcoma, rectal cancer, renal cancer, cancer of the respiratory system, sarcoma, skin cancer, stomach cancer, testicular cancer, thyroid cancer, uterine cancer, cancer of the urinary system and metastasis),

premalignant condition, benign tumor or an infectious disease (e.g. bacterial infection (including an Escherichia coli infection, Staphylococcal infection, a Streptococcal infection, a Pseudomonas infection, Clostridium difficile infection, Legionella infection, Pneumococcus infection, Haemophilus infection, Klebsiella infection, Enterobacter infection, Citrobacter infection, Neisseria infection, Shigella infection, Salmonella infection, Listeria infection, Pasteurella infection, Streptobacillus infection, Spirillum infection, Treponema infection, Actinomyces infection, Borrelia infection, Corynebacterium infection, Nocardia infection, Gardnerella infection, Campylobacter infection, Spirochaeta infection, Proteus infection, Bacteriodes infection, Helicobacter pylori infection, and anthrax infection), mycobacterial infections (including tuberculosis and leprosy), viral infections (e.g. an HIV infection, a Herpes simplex virus 1 infection, a Herpes simplex virus 2 infection, cytomegalovirus infection, hepatitis A virus infection, hepatitis B virus infection, hepatitis C virus infection, human papilloma virus infection, Epstein Barr virus infection, rotavirus infection, adenovirus infection, influenza A virus infection, respiratory syncytial virus infection, varicella-zoster virus infections, small pox infection, monkey pox infection and SARS infection), fungal infections (e.g. candidiasis, ringworm, histoplasmosis, blastomycosis, paracoccidioidomycosis, crytococcosis, aspergillosis, chromomycosis, mycetoma infections, pseudallescheriasis, and tinea versicolor infection) and parasitic infection (e.g. amebiasis, Trypanosoma cruzi infection, Fascioliasis, Leishmaniasis, Plasmodium infections, Onchocerciasis, Paragonimiasis, Trypanosoma brucei infection, Pneumocystis infection, Trichomonas vaginalis infection, Taenia infection, Hymenolepsis infection, Echinococcus infections, Schistosomiasis, neurocysticercosis, Necator americanus infection and Trichuris trichuria infection)), for treating gingivitis, osteomyelitis, diabetes type I, diabetes type II, chronic granuloma, chronic hepatitis B or C infection, chronic EBV infection, chronic Epstein Barr virus infection, multiple sclerosis; for stimulating immune response in a subject at risk of developing cancer due to familiar predisposition (including familial colon polyposis, precancerous polyps, precancerous HPV lesions). (All claimed.)

ADVANTAGE - (I) Increases lymphoid tissue levels of IL-1 (IL-1 alpha or 1 beta), granulocyte-colony stimulating factor (G-CSF) or IL-8 and does not increase serum IL-1 level. The compound shortens the vaccination course by at least one immunization or by at least one day.

Dwg.0/2

TECH UPTX: 20040324

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Method: (M1) Further involves administration of an anticancer therapy other than (I). The anticancer therapy is surgery, radiation or chemotherapy (e.g. aldesleukin, carboplatin, etoposide, **interferon**, interleukin, pentostatin, melphalan, prednisone, taxol and vinorelbine tartrate). (M2) Further involves administration of an anti-microbial agent or microbial antigen. (M3) Additionally involves administration of an adjuvant and treating with the therapy selected from surgery, radiation or chemotherapy. (M4) Further involves administration of antibody or its fragment and an antigen. (M5) Further involves administration of a second active agent (S1).

Preferred Composition: (C1) Additionally comprises a carrier and a housing and instruction of use. In (C1) and (M4), the antibody or its fragment is **conjugated** to a toxin derived from plant, fungus or bacteria (preferably A chain toxin, deglycosylated A chain toxin, ribosome inactivating protein, alpha-sarcin, aspergillin, restictocin, ribonuclease, diphtheria toxin or pseudomonas endotoxin), chemotherapeutic agent (preferably anti-metabolite, an anthracycline, vinca alkaloid, antibiotic alkylating agent or an epipodophyllotoxin) or radioisotope.

(P1) Is provided in a vial or ampoule with a septum. (K1) Further comprise instructions for use. (P2), (K2) and (K4) Is sterile and pyrogen-free and further comprises a carrier. (P2) Comprises distilled water or reverse-osmosis water. (K3) Further comprise instructions for administration of (I). (K4) Further comprises a housing containing the first container and the instructions.

Preferred Components: The antimicrobial agent is an anti-bacterial agent, anti-viral agent, anti-fungal agent, anti-parasitic agent or anti-mycobacterial agent. The anti-bacterial agent is antibiotic, cell wall synthesis inhibitor, cell membrane inhibitor, protein synthesis inhibitor, nucleic acid synthesis or functional inhibitor and competitive inhibitor (preferably natural penicillin, semi-synthetic penicillin, clavulanic acid, cephalosporin, bacitracin, ampicillin, carbenicillin, oxacillin, azlocillin, meslocillin, piperacillin, methicillin, dicloxacillin, nefcillin, cephalothin, cephapirin, cephalexin, cefamandole, cefaclor, cefazolin, cefuroxine, cefoxitin, cefotaxime, cefsulodin, cefetamet, cefixime, ceftriaxone, cefoperazone, ceftazidine, moxalactum, acedapsone, acetosulfone sodium, alamecin, alexidine, amdinocillin, amdinocillin pivoxil, aspartocin, or betamicin sulfate). The antiviral agent is immunoglobulin, amantadine, **interferon**, nucleoside analog, non-nucleoside analog, biflavanoid and protease inhibitor (e.g. AZT, ddC, ddI, D4T, 3TC, acemannan, acyclovir, adefovir, alovudine, alvircept, sudotox, amantadine hydrochloride, aranotin, arildone, atevirdine mesylate, aviridine, cidofovir, desciclovir, didanosine, disoxaril, edoxudine, eviradene or memotine hydrochloride). The anti-fungal agent is e.g. imidazole, amphotericin B, pradimicin, chitinase, acrisorcin, amorolfine, ciclopirox, dipyrithione, itraconazole, octanoic acid and zinoconazole hydrochloride.

The anti-parasitic agent e.g. albendazole, amphotericin B, metrifonate, piperazine, quinacrine HCl, thiadiazole or tryparsamide.

The anti-mycobacterial agent is e.g. isoniazid, rifampin, rifabutin, pyrazinamide, ethambutol, streptomycin, dapsone, amikacin or resorcinomycin A.

The antibody or its fragment is e.g. HER2 antibody (preferably trastuzumab), alemtuzumab (B cell chronic lymphocytic leukemia), gemtuzmnab ozogamicin (CD33+acute myeloid leukemia), hP67.6 (CD33+acute myeloid leukemia), infliximab (inflammatory bowel disease and rheumatoid arthritis), etanercept (rheumatoid arthritis), anti-CD20 antibody (preferably rituximab), tositumomab, MDX-210, oregovomab, anti-EGF receptor mAb, MDX-447, anti-tissue factor protein (TF), edrecolomab, ibritumomab tiuxetan, anti-idiotypic mAb mimic of ganglioside GD3 epitope or anti-HLA-Dr10 mAb. The adjuvant is alum, cholera toxin, CpG immunostimulatory nucleic acids, MPL, MPD or QS-21. The antigen is a cancer antigen or a microbial antigen.

The microbial agent is a bacterial antigen, mycobacterial antigen, viral antigen, fungal antigen or parasitic antigen. The bacterial antigen is derived from E. coli, Staphylococcal, Streptococcal, Pseudomonas, Clostridium difficile, Legionella, Pneumococcus, Haemophilus, Klebsiella, Enterobacter, Citrobacter, Neisseria, Shigella, Salmonella, Listeria, Pasteurella, Streptobacillus, Spirillum, Treponema, Actinomycetes, Borrelia, Corynebacterium, Nocardia, Gardnerella, Campylobacter, Spirochaeta, Proteus, Bacteriodes, H. pylori or anthrax. The mycobacterial antigen is derived from M. tuberculosis and M. leprosy.

The viral antigen is derived from HIV, Herpes simplex virus 1, Herpes simplex virus 2, cytomegalovirus, hepatitis A virus, hepatitis B virus, hepatitis C virus, human papilloma virus, Epstein Barr virus, rotavirus, adenovirus, influenza A virus, respiratory syncytial virus, varicella-zoster virus, small pox, monkey pox and SARS. The fungal antigen is derived from candidiasis, ringworm, histoplasmosis, blastomycosis, paracoccidioidomycosis, crytococcosis, aspergillosis, chromomycosis,

mycetoma infections, pseudallescheriasis, or tinea versicolor infection. The parasitic antigen is derived from amebiasis, Trypanosoma cruzi, Fascioliasis, Leishmaniasis, Plasmodium, Onchocerciasis, Paragonimiasis, Trypanosoma brucei, Pneumocystis, Trichomonas vaginalis, Taenia, Hymenolepsis, Echinococcus, Schistosomiasis, neurocysticercosis, Necator americanus or Trichuris trichuria. The cancer antigen is e.g. MART-1/Melan-A, gp 100, adenosine deaminase-binding protein (ADAbp), cyclophilin b, colorectal associated antigen (CRC)-C017-1A/GA733, MAGE-A1, MAGE-C1, MAGE-Xp4, BAGE, RAGE, LAGE-1, NAG, GnT-V, MUM-1, CDK4, tyrosine, alpha-fetoprotein, E-cadherin, alpha-catenin, beta-catenin, GD2 ganglioside, human papilloma virus proteins, SSX-1, gene or gene product that has undergone chromosomal alteration (e.g. BCL-1 and IgH, BCL-2 and IgH, BCl-6, PARalpha, PML, NPM or PIZF), CD20, CD3/T-cell receptor (TCR), tyrosinase, human leukocyte antigen, HOM-TES-85, HOM-MEL-40 or PRAME.
(S1) Is **IFNalpha**, **pegylated IFN**,
IFNalpha-2b, acyclovir, lobucavir, ganciclovir, L-deoxythymidine, clevudine, a therapeutic vaccine, phosphonoformate, ribavirin, thymosin alpha-1,2,3-dideoxy-3-fluroguanosine, famciclovir, lamivudine, adefovir, dipivoxil, entecavir, emtricitabine or hepatitis B-specific immunoglobulin.
The CDK inhibitor is p21, p27, p57, p15, p16, 018 or p19.
The MMP kinase inhibitor is KY12420(C23H2408), CNI-1493, PD98059, 4-(4-fluorophenyl)-2-(4-methylsulfinylphenyl)-5-(4-pyridyl)1H-imidazole.
The EGFR inhibitor is Tarceva (RTM) (OSI-774), Iressa (RTM) (ZD1839), WHI-P97 (RTM) (quinazoline derivative), LFM-A12 (RTM) (leflunomide metabolite analog) or AG1458 (RTM). The carrier is solubilizer, anti-bacterial preservative (preferably phenylmercuric nitrate, thimerosal, benzetheonium chloride, benzalkonium chloride, phenol, cresol or chlorobutanol), antioxidant (preferably sodium bisulfite) or an adjunct. The carrier has pH of less than 5 (preferably 3-4.5, especially 3 - 4.25, especially 3 - 3.5).
Preferred Compound: (I) Is at least 96 % pure L-isomer.

L22 ANSWER 3 OF 12 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2004-122436 [12] WPIDS
DNC C2004-049152
TI Increasing/maintaining predetermined functional cells in mammal with injured/damaged/deficient of desired cells, without autoimmune disease by injecting composition inducing lymphopenia, increasing desired cell number.
DC A96 B04 D16
IN FAUSTMAN, D
PA (FAUS-I) FAUSTMAN D; (GEHO) GEN HOSPITAL CORP
CYC 103
PI WO 2004003164 A2 20040108 (200412)* EN 126
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PH PL PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG UZ VC VN YU ZA ZM ZW
US 2004028658 A1 20040212 (200412)
ADT WO 2004003164 A2 WO 2003-US20578 20030627; US 2004028658 A1 Provisional US 2002-392687P 20020627, US 2003-358664 20030205
PRAI US 2003-358664 20030205; US 2002-392687P 20020627
AB WO2004003164 A UPAB: 20040218
NOVELTY - Increasing or maintaining the number of functional cells of a predetermined type in a mammal having injured or damaged cells of the predetermined type or mammal having deficiency of cells of the

predetermined type and without an autoimmune disease, comprising administering to mammal a composition that induces lymphopenia and that increases the number of cells of the predetermined cell type in animal.

DETAILED DESCRIPTION - Increasing or maintaining (M1) the number of functional cells of a predetermined type in a mammal having injured or damaged cells of the predetermined type or mammal having deficiency of cells of the predetermined type and without an autoimmune disease or mammal having autoimmune disease or an increased risk for an autoimmune disease, involves administering to mammal a composition that induces lymphopenia and that increases the number of cells of the predetermined cell type in animal or administering to the mammal a composition that kills stimulated blood cells in an amount sufficient to selectively kill a subpopulation of stimulated blood cells in the mammal and administering to the mammal before, after or simultaneous administration of composition with one or more precursor cells that differentiate into cells of the predetermined type in vivo or administering to the mammal one or more cells of predetermined type, preferably blood origin or endothelial origin or administering one or more precursor cells that differentiate one or more cells or predetermined type in vivo and administering to the mammal a composition that kills stimulated or unstimulated blood cells in the mammal or administering to the mammal one or more precursor cells that differentiate into one or more cells of the predetermined type in vivo or that promote proliferation of endogenous cells of the predetermined type in vivo, where the differentiated cell(s) presents MHC class I and peptide, where the MHC class I has at least one allele that matches an MHC class I allele expressed by mammal.

INDEPENDENT CLAIMS are also included for:

(1) treating or stabilizing (M2) an established autoimmune disease in a mammal by administering to the mammal a first composition for one or more times that kills blood cells in an amount sufficient to selectively kill blood cells with increased sensitivity to cell death in the mammal and monitoring the glucose level in the mammal two or more times and/or maintaining the blood glucose level in the mammal within a normal range; and

(2) treating, stabilizing or preventing (M3) a disease, disorder or condition in a mammal, by administering to the mammal a first composition that kills blood cells in an amount sufficient to selectively kill a first subpopulation of unstimulated blood cells in the mammal and administering before, after, simultaneously to the mammal a second composition that kills blood cells in an amount sufficient to selectively kill a second subpopulation of stimulated blood cells in the mammal, where the first subpopulation and the second subpopulation are either partially overlapping subpopulations or non-overlapping subpopulations.

ACTIVITY - Antirheumatic; Antiarthritic; Immunosuppressive; Antianemic; Antithyroid; Antiinflammatory; Vasotropic; Hepatotropic; Dermatological; Antiallergic; Hemostatic; Antipruritic; Auditory; Antipsoriatic; Uropathic; Ophthalmological; Antiulcer; Antidiabetic; Endocrine-Gen.; Muscular-Gen.

Differential effects of complete freund's adjuvant (CFA), Bacillus Clamette-Guerin (BCG), tumor necrosis factor (TNF) - alpha , and splenocyte administration to late stage non-obese diabetic (NOD) mice (15 week of age) were randomly assigned. NOD mice in were in a late pre-diabetic stage of disease at 18 weeks of age with at least one blood sugar greater than 200 mg/dl. NOD mice were subjected to injection of CFA, injection of BCG (4mg/kg), injection of 10 micro g TNF- alpha , or injection of F1 splenocytes (1 multiply 106 cells, IV) obtained from normal donors. The treated NOD mice were serially sacrificed on day 2, day 7, and day 14. An examination of pancreatic histology evaluated the effects CFA, BCG, TNF- alpha , or splenocytes on NOD mice on invasive insulitis. On analysis, on day 2 both a single injection of CFA and a

single injection of low dose TNF- alpha (10 micro g) had eliminated completely all subpopulations of cells with in vitro TNF- alpha sensitivity. At day 7 and day 14, population of TNF- alpha sensitive cells was again evident. Simultaneous pancreatic histology of these cohorts confirmed a dramatic reduction in insulitis, as well as a lingering effect lasting beyond day 14 with respect to insulitis. The therapeutic effect of F1 splenocytes was an elimination of the NOD lymphoid cells, which represented pathogenic naive cells. TNF- alpha sensitivity remained and the F1 splenocyte therapeutic impact lasted beyond day 14. In addition, F1 splenocytes eliminated cords of invasive insulitis per islet effectively.

MECHANISM OF ACTION - Repairing and regenerating damaged tissue.

USE - (M1) is useful for increasing or maintaining the number of functional cells of predetermined type in a mammal, preferably human without autoimmune disease or with an risk of autoimmune disease. (M2) or (M3) is useful in treating, stabilizing or preventing autoimmune disease such as Alopecia areata, Ankylosing spondylitis, Antiphospholipid syndrome, Autoimmune Addison's disease, Autoimmune hemolytic anemia, Autoimmune hepatitis, Behcet's disease, Bullous pemphigoid, Cardiomyopathy, Celiac spru-dermatitis, chronic fatigue immune dysfunction syndrome (CFIDS), chronic inflammatory, demyelinating polyneuropathy, Churg-Strauss syndrome, Cicatricial pemphigoid, CREST syndrome, cold agglutinin disease, Crohn's disease, Discoid lupus, essential mixed cryoglobulinemia, Fibromyalgia-Fibromyositis, Graves' disease, Guillain-Barre, Hashimoto's thyroiditis, hypothyroidism, idiopathi pulmonary, fibrosis, idiopathic thrombocytopenia purpura (ITP), IgA nephropathy, insulin dependent diabetes, Juvenile arthritis, Lichen planus, lupus, Meniere's disease, mixed connective tissue disease, multiple sclerosis, myasthenia gravis, pemphigus vulgaris, pernicious anemia, polyarteritis nodosa, polychondritis, polyglandular syndromes, polymyalgia rheumatica, polymyositis and dermatomyositis, primary agammaglobulinemia, primary billiary cirrhosis, psoriasis, Raynaud's phenomenon, Reiter's syndrome, rheumatic fever, rheumatoid arthritis, sarcoidosis, scleroderma, Sjogren's syndrome, Stiff-Man syndrome, takayasu arteritis, temporal arteritis/giant cell arteritis, ulcerative colitis, uveitis, vasculitis, vitiligo, wegener's granulomatosis, or myasthenia gravis (claimed).

ADVANTAGE - (M1) is efficient in increasing or maintaining the number of functional cells of predetermined type in a mammal. (M2) or (M3) is durable, effective in treating or stabilizing or preventing autoimmune disorders.

Dwg.0/11

TECH UPTX: 20040218

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Method: In (M1), the composition activates a receptor on the surface of cells of predetermined cell type or on the surface of precursor cells that differentiate into cells of the predetermined cell type in the mammal. (M1) also inducing damage to the cells of a predetermined type in the mammal or inducing damage in a site of the mammal in which cells of the predetermined type are desirable. The precursor cells are stem cells. The cells of predetermined type are islet cells that produce insulin, blood cells, spleen cells, chondrocytes, brain cells, heart cells, vascular tissue cells, cells of the bile duct, epithelial cells, endothelial cells, endoderm cells, mesoderm cells, mesenchymal cells, cells of mesenchymal origin, or skin cells. The cells that differentiate into cells of predetermined type in vivo are splenocytes, bone marrow derived cells, Hoechst 33342 positive cells, brain cells, CNS positive cells, hepatocytes, or fetal cells. The cells that differentiate into cells of predetermined type in vivo are semi-allogeneic and to express Fas or FasL. The blood cells are T-cells, B-cells, or macrophages. The composition is MHC class I and peptide, where the MHC class I has at least one allele

that matches an MHC class I allele expressed by the mammal. The MHC class I and peptide are semi-allogeneic or isogeneic.
The composition is a compound that crosslinks a T-cell receptor (TCR) of naive T cells or the composition is TNF-alpha, a TNF-alpha agonist, or a TNF-alpha inducing substances. The composition binds or activates a death receptor. The TNF-alpha inducing substance is complete freund's adjuvant (CFA), ISS-ODN, microbial adjuvants, such as cell wall components with LPS-like activity, cholera particles, Escherichia coli heat labile enterotoxin, E.coli heat labile enterotoxin complexed with lecithin vesicles, ISCOMS-immune stimulating complexes, chemical adjuvants, such as **polyethylene glycol** and poly(N-2-(hydroxypropyl)methacrylamide), synthetic oligonucleotides containing CpG or CpA motifs, lipid A derivatives, such as monophosphoryl lipid A, MPL, muramyl **dipeptide** derivatives, Bacillus Clamette-Guerin, tissue plasminogen activator, LPS, interleukin-1, interleukin-2, UV light, lymphotoxin, cachectin, a TNFR-2 agonist, an intracellular mediator of the TNF-alpha signaling pathway, a NFkB inducing substance, lymphotoxin, cachectin, IRF-1, STAT1, an agonist of an ICS-2lgAS promoter elements, lymphokine, or the combination of TNF-alpha and a TNFR-1 antibody.
(M1) further involves administering to mammal a proteasome activity promoting substance, preferably gamma **interferon** or administering to a mammal an agent that increases Flk or Flt expression or function or administering to a mammal an agent that increases VEGF, VEGF1, VEGF2, VEGF1R, or VEGF2R expression or function, preferably the agent is a VEGF polypeptide or a nucleic acid molecule encoding a VEGF polypeptide or administering to a mammal to an inhibitor of Fas or FasL expression or signaling, where the mammal has an autoimmune disease or an increased risk for an autoimmune disease or metabolic disorder that is due to the injury or damage of the cells, of a predetermined type or due to autoimmune disease is controlled. (M1) further involves maintaining the blood glucose level in mammal within a normal range. (M1) further involves administering a cytokine, chemokine, or growth factor to mammal.
(M2) further involves administering to the mammal a second composition that kills blood cells in an amount sufficient to selectively kill blood cells with increased sensitivity to the cell death in the mammal and determining whether the mammal has a subpopulation of blood cells with increased sensitivity to the first composition before administration of first composition.
In (M3), the first subpopulation and the second subpopulation are in different stages of differentiation or in different stages of the cell cycle. The first subpopulation and second subpopulation are sensitive to different inducers of cell death and undergo cell death through different pathways, preferably one subpopulation undergoes cell death through apoptosis and the other subpopulation undergoes cell death through necrosis. (M3) further involves administering to the mammal one or more cells that have the potential to differentiate into one or more cells of predetermined type or that are of the predetermined cell type or administering a cell that promotes proliferation of precursor cells or cells of predetermined cell type, preferably cells are endothelial cells.

L22 ANSWER 4 OF 12 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2004-099189 [10] WPIDS
DNC C2004-041019
TI Composition comprising an agent and/or antibody or its fragment, useful for treating auto-immune disease, thrombosis, restenosis, metastasis, or for inhibiting growth and/or replication of tumor cells or leukemia cells.
DC B04 D16 K08
IN HOCH-MAR-CHAIM, H; LAZAROVITS, J; LEVANON, A; NIMROD, A
PA (SAVI-N) SAVIENT PHARM INC
CYC 103

PI WO 2004002528 A1 20040108 (200410)* EN 58
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS
LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK
DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR
KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PG PH PL
PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG UZ VC VN YU
ZA ZM ZW
ADT WO 2004002528 A1 WO 2003-US20604 20030630
PRAI US 2002-189025 20020701
AB WO2004002528 A UPAB: 20040210
NOVELTY - A composition (I) comprising an agent and an antibody, or its fragment, is new.

DETAILED DESCRIPTION - AN INDEPENDENT CLAIMS is also included for treatment (M1) comprising administering to a patient in need, an antibody or its fragment, and an agent, one or both of the antibody, or its fragment, and/or the agent is administered in a sub-clinical amount.

ACTIVITY - Cytostatic; Immunosuppressive; Antiinflammatory; Vasotropic; Anticoagulant; Thrombolytic.

MECHANISM OF ACTION - Antibody therapy; Antibody acts synergistically with chemotherapy to enhance the survival rate.

Interaction between chemotherapy treatment and Y1 (antibody) in the MOLT-4 tumor-bearing mice was studied as follows. SCID mice were pretreated with 100 mg/kg cytoxan-cyclophosphamid for injection (CTX). Five days after CTX injection, MOLT-4 cells were inoculated intravenously (i.v.) through the tail vein with 2 multiply 107 cells. Mice were randomly divided into 5 treatment groups (13 per group), and they were treated, beginning 5 days after cell inoculation. Tumor-bearing mice were treated for two weeks with sub-optimal dose of doxorubicin (Dox), in combination with Y1 given either concomitantly or after the Dox course of treatment. The response to the therapies was monitored as survival. The results indicate that treatment with a sub-optimal dose of Dox, had a negative effect on the survival of tumor-bearing mice (the mean survival time (MST) is 33.5 plus or minus 1.68 days), relative to the control group (MTS 39.08 plus or minus 0.8 days). However, the survival of mice sequentially treated with Dox, followed by Y1, was highly significantly prolonged. Although Y1 alone had a dramatic effect on the survival rate of tumor-bearing mice, combination of sub-clinically optimal Dox+Y1 had the best effect. The significantly increased survival rate appears to be the result of a synergistic effect between chemotherapy and the Y1 antibody.

USE - (I) is useful for inhibiting cell rolling, inflammation, auto-immune disease, thrombosis, restenosis, metastasis, growth and/or replication of tumor cells, increasing the mortality rate of tumor cells, inhibiting growth and/or replication of leukemia cells, increasing the mortality rate of leukemia cells, increasing the susceptibility of diseased cells to damage by anti-disease agent, increasing the susceptibility of tumor cells to damage by anti-cancer agents, increasing the susceptibility of leukemia cells to damage by anti-cancer agents, inhibiting increase in number of tumor cells in a patient having a tumor, decreasing number of tumor cells in a patient having a tumor, inhibiting increase in number of leukemia cells in a patient having leukemia, decreasing number of leukemia cells in a patient, inhibiting cell-cell, cell-matrix, platelet-matrix, platelet-platelet, and/or cell-platelet complex formation, ameliorating the effects of a disease, preventing a disease, treating a disease, or inhibiting the progress of a disease. In (I), the sub-clinical amount of the agent is insufficient to inhibit effectively cell rolling, inflammation, auto-immune disease, thrombosis, restenosis, metastasis, or growth and/or replication of tumor cells or leukemia cells, or to increase in the number of tumor cells in a patient having a tumor or inhibit an increase in the number of leukemia cells in a

patient having leukemia, or to decrease the number of tumor cells in a patient having a tumor or decrease the number of leukemia cells in a patient having leukemia, or to increase mortality of tumor cells or leukemia cells, increase susceptibility of tumor cells to damage by anti-cancer agents, or increase susceptibility of leukemia cells to damage by anti-leukemia agents. The sub-clinical amount of the agent is sufficient to inhibit effectively cell-cell, cell-matrix, platelet-matrix, platelet-platelet, and/or cell-platelet complex formation, aggregation, or adhesion (claimed).

DESCRIPTION OF DRAWING(S) - The figure shows graphical representation of percent survival of MOLT-4 tumor-bearing mice as a function of time (days) following administration of doxorubicin and Y1 alone, sequentially, or in combination.

Dwg.1/1

TECH UPTX: 20040210

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Composition: In (I), the agent is complexed with the antibody, or its fragment. The agent combined or **conjugated** is present in a sub-clinical amount. The sub-clinical amount of the agent is insufficient to alter effectively the susceptibility of diseased cells by anti-disease agents. The sub-clinical amount of the agent is insufficient to alter effectively the susceptibility of diseased cell but anti-disease agents. In (I), the antibody, or its fragment is present in a sub-clinical amount. The antibody or its fragment has the binding capabilities of an scFv antibody fragment of a fully defined Y1, Y17, L32 sequences of 277, 278, 280 amino acids respectively as given in the specification. The antibody or its fragment has the binding capabilities of a peptide or polypeptide, where the peptide or polypeptide comprises a first hypervariable region having a sequence of **Met**-Arg-**Ala**-Pro-Val-Ile. The peptide or polypeptide further comprising a second hypervariable region having a sequence of Gly-Ile-Asn-Trp-Asn-Gly-Gly-Ser-Thr-Gly-Tyr-Ala-Asp-Ser-Val-Lys and/or a third hypervariable region having a sequence of Asp-Trp-Gly-Met-Ser, Leu-Thr-His-Pro-Tyr-Phe or Leu-Asn-Pro-Lys-Val-Lys-His-Met. The antibody or its fragment is an scFv or an Fab fragment. (I) preferably comprises an agent and an antibody, or its fragment, where the antibody or its fragment binds to a peptide or polypeptide epitope of about 3 to 126 amino acid residues in length, where the peptide or polypeptide epitope has at least 2 acidic amino acids and at least one sulfated tyrosine residue. (I) preferably comprises an agent and an antibody, or its fragment, where the antibody or its fragment, binds to at least two different molecules chosen from PSGL-1, fibrinogen gamma prime (gamma), GP1balpha, heparin, lumican, complement compound 4 (CC4), inter alpha inhibitor, and prothrombin and that binds to at least one cell type chosen from the group consisting of B cell leukemia cells, B-CLL cells, AML cells, multiple myeloma cells, and metastatic cell. (I) preferably comprises an agent and an antibody, or its fragment, cross-reacts with two or more epitopes, each epitope comprising one or more sulfated tyrosine residues and at least one cluster of two or more acidic amino acids. The agent is chosen from anti-cancer, anti-metastasis, anti-leukemia, anti-disease, anti-adhesion, anti-thrombosis, anti-restenosis, anti-autoimmune, anti-aggregation, anti-bacterial, anti-viral, and anti-inflammatory agents. The agent is an anti-viral agent chosen from acyclovir, ganciclovir and zidovudine. The agent is an anti-inflammatory agent chosen from zaltoprofen, pranoprofen, droxicam, acetyl salicylic 17, diclofenac, ibuprofen, dexibuprofen, sulindac, naproxen, amtolmetin, celecoxib, indomethacin, rofecoxib, and nimesulid. The agent is anti-autoimmune agent chosen from leflunomide, denileukin difitox, subreum, WinRho SDF, defibrotide and cyclophosphamide. The agent is anti-adhesion/anti-aggregation agent chosen from limaprost, clorcromenet, and hyaluronic acid. The agent is chosen from toxins, radioisotopes, and

pharmaceutical agents. The toxin is chosen from gelonin, Pseudomonas exotoxin (PE), PE40, PE38, ricin, and modification and their derivatives. The radioisotope is chosen from gamma-emitters, positron-emitters, x-ray emitters, beta-emitters, and alpha-emitters. The radioisotope is chosen from 111indium, 113 indium, 99mrhenium, 105rhenium, 101rhenium, 99mtechnetium, 121mtellurium, 122mtellurium, 125mtellurium, 165thulium, 167thulium, 168thulium, 123iodine, 126iodine, 131iodine, 133iodine, 81mkrypton, 33xenon, 90yttrium, 213bismuth, 77bromine, 18fluorine, 95ruthenium, 97ruthenium, 103ruthenium, 105ruthenium, 107mercury, 203mercury, 67gallium and 68gallium. The pharmaceutical agent is chosen from cis-platinum, taxol, calicheamicin, vincristine, cytarabine (Ara-C), cyclophosphamide, prednisone, fludarabine, chlorambucil, **interferon** alpha, hydroxy urea, temozolomide, thalidomide and bleomycin, and its derivatives and combinations. The pharmaceutical agent is an anthracycline or its derivatives. The pharmaceutical agent is chosen from doxorubicin, daunorubicin, idarubicin, morpholinodoxorubicin, morpholinodaunorubicin, methoxymorpholinyldoxorubicin, and its derivatives and combinations. The agent is doxorubicin and its derivatives. The antibody or its fragment is coupled to or complexed with a vehicle or carrier that is coupled to or complexed or combined with more than one agent. The vehicle or carrier is chosen from dextran, lipophilic **polymers**, hydrophilic **polymers**, HPMA, and liposomes. The vehicle or carrier is a doxorubicin-decorated liposomes. The vehicle is **polyethylene glycol** (**PEG**) or dextran.
Preferred Method: In (M1), the antibody or its fragment, and the agent are administered separately. The antibody or its fragment is administered prior to the agent, subsequent to the agent.

L22 ANSWER 5 OF 12 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2003-587260 [55] WPIDS
DNC C2003-158925
TI Inducing an immune response in humans against autologous carcinoembryonic antigen (CEA) comprises administering a modified CEA polypeptide, a nucleic acid encoding the polypeptide, or a microorganism expressing the polypeptide.
DC B04 D16
IN KLYSNER, S; VOLDBORG, B
PA (PHAR-N) PHARMEXA AS
CYC 102
PI WO 2003059379 A2 20030724 (200355)* EN 140
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT SD SE SI SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
AU 2003203140 A1 20030730 (200421)
ADT WO 2003059379 A2 WO 2003-DK31 20030117; AU 2003203140 A1 AU 2003-203140 20030117
FDT AU 2003203140 A1 Based on WO 2003059379
PRAI US 2002-350047P 20020117; DK 2002-82 20020117
AB WO2003059379 A UPAB: 20030828
NOVELTY - Inducing an immune response against autologous carcinoembryonic antigen (CEA) in an animal, e.g. human, comprises effecting uptake and processing by antigen presenting cells (APCs) in the animal of at least 1 modified CEA polypeptide or of a nucleic acid encoding the modified CEA polypeptide or of a microorganism or virus expressing the modified CEA polypeptide to induce a CTL response and an antibody response that targets the autologous CEA.

DETAILED DESCRIPTION - Inducing an immune response against autologous carcinoembryonic antigen (CEA) in an animal, e.g. human, comprises effecting uptake and processing by antigen presenting cells (APCs) in the animal of at least 1 modified CEA polypeptide or of a nucleic acid encoding the modified CEA polypeptide or of a microorganism or virus expressing the modified CEA polypeptide to induce a CTL response and an antibody response that targets the autologous CEA. The at least one modified CEA polypeptide comprises at least about 80 CEA-derived amino acids, either in the form of at least about 80 consecutive CEA-derived amino acids or in the form of at least about 80 amino acids constituted of uninterrupted CEA-derived CTL epitopes, and at least one first T-helper epitope (TH epitope) foreign to the animal.

INDEPENDENT CLAIMS are included for:

(1) a modified human CEA polypeptide cited above, which is capable of inducing an immune response against autologous CEA in a human subject;

(2) a nucleic acid fragment encoding the above modified CEA polypeptide;

(3) a vector carrying the nucleic acid fragment cited above;

(4) a transformed cell carrying the vector;

(5) an immunogenic composition comprising, as an effective immunogenic agent, the above modified human CEA, nucleic acid fragment or vector in admixture with a carrier, diluent or vehicle, and optionally an adjuvant;

(6) a stable cell line carrying the vector and expressing the above nucleic acid fragment and, optionally, secreting or carrying the modified CEA on its surface; and

(7) a method for preparing the above cell line, comprising transforming a host cell with the nucleic acid fragment or with the vector.

ACTIVITY - Cytostatic.

No biological data given.

MECHANISM OF ACTION - Vaccine.

USE - The method is useful in immunizing actively against diseases characterized by cells that express CEA.

Dwg.0/2

TECH UPTX: 20030828

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Method: In inducing an immune response against autologous CEA in a human being, the modified CEA polypeptide comprises at least about 100 (preferably at least about 500) CEA derived amino acids. The CEA-derived CTL epitope is presented by the APC in association with a Major Histocompatibility Complex (MHC) Class I molecule on the surface of the APC and/or where the first foreign TH epitope is presented by an APC in association with an MHC Class II molecule on the surface of the APC. The APC is a dendritic cell or a macrophage. The modified CEA polypeptide is in the form of one first analogue of CEA, the first analogue comprising a variation of the amino acid sequence of CEA, where the variation contains CEA-derived CTL epitope(s) and the first foreign TH epitope. The first analogue contains a substantial fraction of known and predicted CTL epitopes from autologous CEA. The substantial fraction of known and predicted CTL epitopes in the amino acid sequence of the analogue are recognized by at least 90% of the MHC-I haplotypes recognizing all known and predicted CTL epitopes in CEA. The substantially all known CTL epitopes of the autologous CEA are present in the first analogue and/or where substantially all predicted CTL epitopes of the autologous CEA are present in the first analogue. The first analogue further comprises at least one B-cell epitope of the autologous CEA, so that immunization of the animal with the first analogue induces production of antibodies in the animal against the autologous CEA. One modified CEA polypeptide is in the form of at least one second analogue of the autologous CEA, the second analogue containing at least

one B-cell epitope of the autologous CEA, so that immunization of the animal with the second analogue induces production of antibodies against the autologous CEA. The second foreign TH epitope is included in the second analogue. The first and/or second analogue(s) comprise(s) a substantial fraction of the B-cell epitopes of the autologous CEA. The modified CEA polypeptide substantially includes the amino acid sequence of at least one domain, such as at least 2, 3, 4, 5, 6 or all 7 domains of CEA. Additionally, the modified CEA polypeptide can be provided by subjecting CEA to amino acid substitution and/or deletion and/or insertion and/or addition. The modified CEA polypeptide comprises at least one first moiety effecting targeting of the modified CEA polypeptide to an APC and/or at least one second moiety stimulating the immune system, and/or at least one third moiety optimizing presentation of the modified CEA to the immune system. The polypeptide includes duplication of at least one B-cell epitope or of at least one CTL epitope of the autologous CEA. The first and/or, where applicable, second foreign TH epitope(s) is/are immunodominant and/or promiscuous. The modified CEA polypeptide is provided by introduction of a foreign TH epitope that is introduced in any one of the following regions of CEA: in the C-terminus, in the N-terminus, in the loop structures in any one of domains 1-7 listed in the specification, and between any two adjacent domains of CEA. The foreign TH epitope is introduced as an addition to the C- or N-terminus of mature CEA; as an insertion before any one of CEA amino acids 1, 38, 39, 40, 41, 42, 111, 148, 149, 150, 151, 203, 326, 327, 328, 329, 381, 418, 419, 420, 421, 464, 504, 505, 506, 507, 559, 596, 597, 598 and 643; and as a substitution that includes deletion of any one or all of amino acids 38, 39, 40, 41, 148, 149, 150, 326, 327, 328, 418, 419, 420, 504, 505, 506, 596 and 597, where the amino acid numbering corresponds to a sequence fully defined in the specification. The C-terminal GPI-anchor of CEA is preserved in the modified CEA polypeptide. Alternatively, the C-terminal GPI-anchor of CEA is removed. The foreign TH epitope(s) is/are selected from a natural TH epitope and an artificial MHC-II binding peptide sequence. The natural T-cell epitope is selected from a Tetanus toxoid epitope, a diphtheria toxoid epitope, an influenza virus hemagluttinin epitope and a Plasmodium falciparum CS epitope. The non-CEA derived components such as foreign TH epitopes or first, second and third moieties are present in the form of side groups attached covalently or non-covalently to suitable chemical groups in the amino acid sequence of the autologous CEA, or its subsequence, and/or fusion partners to the amino acid sequence derived from the autologous CEA. The first moiety is a substantially specific binding partner for an APC specific surface antigen, such as a carbohydrate for which there is a receptor on the APC, e.g. mannan or mannose, or where the first moiety is a hapten. The second moiety is a cytokine selected from **interferon** gamma (**IFN** -c); Flt3L; interleukin (IL)1; IL-2; IL-4; IL-6; IL-12; IL-13; IL-15; granulocyte-macrophage colony stimulating factor (GM-CSF) or its part; a heatshock protein selected from heat shock protein 70 (HSP70), HSP90, heat shock cognate 70 (HSC70), glucose-regulated protein 94 (GRP94), calreticulin (CRT) or its part; or a hormone. The third moiety is a lipid such as a palmitoyl group, a myristyl group, a farnesyl group, a geranyl-geranyl group, a GPI-anchor, or an N-acyl diglyceride group. The modified CEA polypeptide substantially preserves the 3-dimensional structure of at least one of CEA domains 1-7. The 3-dimensional structures of at least 4 of CEA domains 1-7 is substantially preserved, preferably those of domains 1-4. Alternatively, the 3-dimensional structures of all CEA domains are substantially preserved. The above method comprises administering to the animal an amount of the modified CEA polypeptide. The modified CEA is formulated together with a carrier and/or vehicle and, optionally, an adjuvant. The adjuvant is selected from an immune targeting adjuvant; an immune modulating adjuvant such as a toxin, a cytokine and a

mycobacterial derivative; an oil formulation; a polymer; a micelle forming adjuvant; a saponin; an immunostimulating complex matrix (ISCOM matrix); a particle; DDA; aluminum adjuvants; DNA adjuvants; gamma-inulin; and an encapsulating adjuvant. The toxin is selected from listeriolycin (LLO), Lipid A (MPL, L180.5/RalLPS) and heat-labile enterotoxin. The mycobacterial derivative is selected from muramyl **dipeptide**, complete Freund's adjuvant, RIBI and a diester of trehalose such as TDM and TDE. The immune targeting adjuvant is selected from CD40 ligand, CD40 antibodies or their specifically binding fragments, mannose, a Fab fragment and CTLA-4. The oil formulation comprises squalene or incomplete Freund's adjuvant. The polymer is selected from a carbohydrate such as dextran, **PEG**, starch, mannan, and mannose; a plastic polymer and latex such as latex beads. The saponin is Quillaja saponaria saponin, Quil A or QS21. The particle comprises latex or dextran. The method also comprises administering to the animal the nucleic acid fragment that encodes and expresses the modified CEA polypeptide, or a non-pathogenic microorganism or virus carrying the nucleic acid fragment. The non-pathogenic microorganism or virus is administered once to the animal. The nucleic acid fragment is selected from naked DNA, DNA formulated with charged or uncharged lipids, DNA formulated in liposomes, emulsified DNA, DNA included in a viral vector, DNA formulated with a transfection-facilitating protein or polypeptide, DNA formulated with a targeting protein or polypeptide, DNA formulated with a targeting carbohydrate, DNA formulated with Calcium precipitating agents, DNA coupled to an inert carrier molecule, and DNA formulated with an adjuvant.
Preferred Vector: The vector is capable of autonomous replication. It is selected from a plasmid, a phage, a cosmid, a mini-chromosome, and a virus. The vector comprises, in the 5'-3' direction and in operable linkage, a promoter for driving expression of the nucleic acid fragment, optionally a nucleic acid sequence encoding a leader peptide enabling secretion of or integration into the membrane of the polypeptide fragment, the nucleic acid fragment cited above, and optionally a nucleic acid sequence encoding a terminator. The vector, when introduced into a host cell, is integrated in the host cell genome or is not capable of being integrated in the host cell genome.

L22 ANSWER 6 OF 12 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2002-759837 [82] WPIDS
DNC C2002-214753
TI New Major Histocompatibility Complex (MHC) molecule construct, useful for treating, preventing, stabilizing or alleviating a disease involving MHC recognizing cells e.g., cancer.
DC B04 D16
IN AMELLEM, O; BUUS, S; PETERSEN, L O; RUUD, E; SCHOLLER, J; WINTHER, L; AAMELLEM, O; RUUB, E; SCHOELLER, J
PA (DAKO-N) DAKOCYTOMATION DENMARK AS; (DYNA-N) DYNAL BIOTECH ASA
CYC 101
PI WO 2002072631 A2 20020919 (200282)* EN 304
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW
NO 2003004020 A 20031106 (200380)
EP 1377609 A2 20040107 (200404) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR
ADT WO 2002072631 A2 WO 2002-DK169 20020313; NO 2003004020 A WO 2002-DK169

20020313, NO 2003-4020 20030911; EP 1377609 A2 EP 2002-706685 20020313, WO 2002-DK169 20020313

FDT EP 1377609 A2 Based on WO 2002072631

PRAI US 2001-275470P 20010314; DK 2001-435 20010314;
DK 2001-436 20010314; DK 2001-441 20010314;
US 2001-275447P 20010314; US 2001-275448P 20010314

AB WO 200272631 A UPAB: 20021220

NOVELTY - A new Major Histocompatibility Complex (MHC) molecule construct comprising a carrier molecule to which one or more MHC molecules are attached either directly or via one or more entities, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) detecting the presence or MHC recognizing cells in a sample;

(2) monitoring MHC recognizing cells;

(3) establishing a prognosis of a disease involving MHC recognizing cells;

(4) determining the status of, or the effectiveness of a medicament against, a disease involving MHC recognizing cells;

(5) diagnosing a disease involving MHC recognizing cells;

(6) a therapeutic composition comprising as active ingredient a MHC molecule construct;

(7) up-regulating, down-regulating or modulating an immune response in an animal, including a human being;

(8) treating an animal, including a human being;

(9) inducing energy of a cell in animal, including a human being;

(10) an adoptive cellular immunotherapeutic method;

(11) obtaining MHC recognizing cells; or

(12) producing a therapeutic composition.

ACTIVITY - Cytostatic; Antiinflammatory; Dermatological; Antiasthmatic; Antidiabetic; Anti-HIV; Virucide; Antiarteriosclerotic; Antiulcer; Antirheumatic; Antiarthritic; Antipsoriatic; Immunosuppressive. No biological data is given.

MECHANISM OF ACTION - Gene therapy.

USE - The MHC molecule construct is useful as a therapeutic composition in in vivo or ex vivo therapy, for treating, preventing, stabilizing or alleviating a disease involving MHC recognizing cells, for monitoring MHC recognizing cells or establishing a prognosis of a disease or diagnosing a disease, or determining the status of a disease or the effectiveness of a medicament against a disease, involving MHC recognizing cells, e.g., chronic inflammatory bowel disease such as Crohn's disease or ulcerative colitis, sclerosis, type I diabetes, rheumatoid arthritis, psoriasis, atopic dermatitis, asthma, malignant melanoma, renal carcinoma, breast cancer, lung cancer, cancer of the uterus, cervical cancer, prostate cancer, brain cancer, head and neck cancer, leukemia, cutaneous lymphoma, hepatic carcinoma, colorectal cancer, bladder cancer, rejection-related disease, Graft-versus-host-related disease, or a viral disease associated with hepatitis, Acquired Immunodeficiency Syndrome (AIDS), measles, pox, chicken pox, rubella or herpes. The MHC molecule construct is also useful for flow cytometric, histological or cytological method (all claimed.)

Dwg.0/57

TECH UPTX: 20021220

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Construct: The MHC molecule construct is in soluble form in a solubilizing medium. It is immobilized directly onto a biodegradable solid or semi-solid support via a linker, a spacer, or antibody or antibody derivative or its fragment, prior to expansion. The expansion is carried out in the presence of one or more MHC molecule constructs, optionally one or more biologically active molecules and optionally feeder cells such as dendritic cells or feeder cells. The support is selected from glass or chamber slides, dishes or petridishes

microtiter plates having one or more wells, particles, beads, biodegradable particles, sheets, gels, filters, membranes (e. g. nylon or **polymer** membranes), fibers, capillaries, needles, microtiter strips, tubes, plates or wells, combs, pipette tips, micro arrays or chips. Preferably, the support is selected from beads and particles, which are **polymeric** beads, **polymeric** particles, magnetic beads, magnetic particles, supermagnetic beads or particles. The MHC molecule construct comprises peptide free or filled MHC molecules. The total number of MHC molecules of the construct is from 1 - 25, 1 - 50 or 1 - 100. The peptides to fill the peptide free MHC molecules, and the MHC molecule construct comprising peptide free molecules are provided separately. The MHC molecule construct further comprises one or more biologically active molecules selected from proteins, co-stimulatory molecules, cell modulating molecules, receptors, accessory molecules, adhesion molecules, natural ligands, toxic molecules, antibodies, recombinant binding molecules or their combinations. The biologically active molecules also comprises:

(1) proteins such as MHC Class I-like proteins like MIC A, MIC B, CD1d, human leukocyte antigen (HLA) E, HLA F, HLA G, HLA H, ULBP-1, ULBP-2, and ULBP-3;

(2) co-stimulatory molecules such as CD2, CD3, CD4, CD5, CD8, CD9, CD27, CD28, CD30, CD69, CD134 (OX40), CD137 (4-1BB), CD147, CDw150 (SLAM), CD152 (CTLA-4), CD153 (CD30L), CD40L (CD154), NKG2D, ICOS, HVEM, HLA Class II, PD-1, Fas (CD95), FasL expressed on T and/or NK cells, CD40, CD48, CD58, CD70, CD72, B7.1 (CD80), B7.2 (CD86), B7RP-1, B7H3, PD-L1, PD-L2, CD134L, CD137L, ICOSL, LIGHT expressed on APC and/or tumor cells;

(3) cell modulating molecules such as CD16, NKp30, NKp44, NKp46, NKp80, 2B4, KIR, LIR, CD94/NKG2A, CD94/NKG2C expressed on natural killer (NK) cells, **interferon** (**IFN**)-alpha, **IFN**-beta, **IFN**-gamma, interleukin (IL)-1, IL-2, IL-3, IL-4, IL-6, IL-7, IL-8, IL-10, IL-11, IL-12, IL-15, CSFs (colony-stimulating factors), vitamin D3, IL-2 toxins, cyclosporin, FK-506, rapamycin, transforming growth factor (TGF)-beta, clotrimazole, nitrendipine, and charybdotoxin, accessory molecules such as lymphocyte function associated molecule (LFA)-1, CD11a/18, CD54 (intercellular adhesion molecule (ICAM)-1) CD106 (VCAM), and CD49a,b,c,d,e,f/CD29 (VLA-4);

(4) adhesion molecules such as ICAM-1, ICAM-2, GlyCAM-1, CD34, anti-LFA-1, anti-CD44, anti-beta7, chemokines, CXCR4, CCR5, anti-selectin L, anti-selectin E, and anti-selectin P;

(5) toxic molecules such as cyclophosphamide, methrotrexate, Azathioprine, mizoribine, 15-deoxuspergualin, neomycin, staurosporine, genestein, herbimycin A, Pseudomonas exotoxin A, saporin, Rituxan, Ricin, gemtuzumab ozogamicin, Shiga toxin, heavy metals like inorganic and organic mercurials, and FN18-CRM9, radioisotopes such as incorporated isotopes of iodide, cobalt, selenium, tritium, and phosphor, and haptens such as DNP, and digoxiginin; or

(6) antibodies or antibody derivatives or fragments, or combinations of (1) - (5).

The MHC molecule construct further comprises one or more labeling compounds that are attached to the carrier molecule, one or more of the binding entities or one or more of the MHC molecules. The labeling compound, which is directly or indirectly detectable, is a fluorescent label, an enzyme label, a radioisotope, a chemiluminescent label, a bioluminescent label, a **polymer**, a metal particle, a hapten, an antibody or a dye. It is selected from:

(1) fluorescent labels such as 5-(and 6)-carboxyfluorescein, 5- or 6-carboxyfluorescein, 6-(fluorescein)-5-(and 6)-carboxamido hexanoic acid, fluorescein isothiocyanate (F)TC), rhodamine, tetramethylrhodamine, and dyes such as Cy2, Cy3 and Cy5, optionally substituted coumarin including AMCA, PerCP, phycobiliproteins including R-phycoerythrin (RPE) and

allophycoerythrin (APC), Texas Red, Princeston Red, Green fluorescent protein (GFP) and their analogs, and **conjugates** of R-phycoerythrin or allophycoerythrin and e.g. Cy5 or Texas Red, and inorganic fluorescent labels based on semiconductor nanocrystals (like quantum dot and Qdot (RTM) nanocrystals), and time-resolved fluorescent labels based on lanthanides like Eu3+ and Sm3+;
(2) haptens such as DNP, biotin, and digoxiginin;
(3) enzymatic labels such as horse radish peroxidase (HRP), alkaline phosphatase (AP), betagalactosidase (GAL), glucose-6-phosphate dehydrogenase, beta-N-acetylglucosaminidase, beta-glucuronidase, invertase, Xanthine Oxidase, firefly luciferase and glucose oxidase (GO);
(4) luminescence labels such as luminol, isoluminol, acridinium esters, 1,2-dioxetanes and pyridopyridazines; or
(5) radioactivity labels such as incorporated isotopes of iodide, cobalt, selenium, tritium, and phosphor.
The carrier molecule, which is soluble molecule, consists of:
(1) polysaccharides including dextrans, carboxy methyl dextran, dextran polyaldehyde, carboxymethyl dextran lactone, and cyclodextrins, pullulans, schizophyllan, scleroglucan, xanthan, gellan, O-ethylamino guaran, chitins and chitosans including 6-0- carboxymethyl chitin and N-carboxymethyl chitosan;
(2) derivatized cellolosics including carboxymethyl cellulose, carboxymethyl hydroxyethyl cellulose, hydroxy-ethyl cellulose, 6-amino-6-deoxy cellulose and O-ethyl-amine cellulose;
(3) hydroxylated starch, hydroxypropyl starch, hydroxyethyl starch, carrageenans, alginates, and agarose, synthetic polysaccharides including ficoll and carboxy-methylated ficoll;
(4) vinyl **polymers** including poly(acrylic acid), poly(acrylamides), poly(acrylic esters), poly(2-hydroxy ethyl meth-acrylate), poly(methyl methacrylate), poly(maleic acid), poly(maleic anhydride), poly(acrylamide), poly(ethyl-co-vinyl acetate), poly(methacrylic acid), poly(vinyl-alcohol), poly(vinyl alcohol-co-vinyl chloroacetate), aminated poly(vinyl alcohol), and their co block **polymers**;
(5) **poly ethylene glycol** (**PEG**) or polypropylene glycol or poly(ethylene oxide-co-propylene oxides) containing **polymer** backbones including linear, comb-shaped or StarBurst (RTM) dendrimers;
(6) poly amino acids including polylysines, polyglutamic acid, polyurethanes, poly(ethylene imines), pluriol;
(7) proteins including albumins, immunoglobulins, and virus-like proteins (VLP); or
(8) polynucleotides, DNA, PNA, LNA, oligonucleotides or oligonucleotide dendrimer constructs.
The MHC molecule is a vertebrate MHC molecule such as a human, murine, rat, porcine, bovine or avian molecule. Preferably the MHC molecule is a human MHC molecule. It is a peptide free MHC molecule. The MHC molecule comprises:
(1) a MHC Class I molecule consisting of a heavy chain, a heavy chain combined with a beta2m, a heavy chain combined with a peptide or a heavy chain/beta2m dimer with a peptide;
(2) a MHC Class II molecule consisting of an alpha/beta dimer, an alpha/beta dimer with a peptide, alpha/beta dimer combined through an affinity tag and an alpha/beta dimer combined through an affinity tag with a peptide; or
(3) a MHC Class I like molecule or MHC Class II like molecule.
Two of the MHC molecules or the peptides harbored by the MHC molecules are either the same or different. The MHC molecules are attached to the carrier molecule directly or via one or more binding entities. 1 - 2, 1 - 3, 1 - 4, 1 - 6, 1 - 8 or 1 - 10 MHC molecules are attached to the carrier

molecule by each binding entity. The binding entity is selected from streptavidin (SA) and avidin or their derivatives, biotin, immunoglobulins, antibodies (monoclonal, polyclonal, and recombinant), antibody fragments and their derivatives, leucine zipper domain of AP-1 (jun and fos), hexa-his (metal chelate moiety), hexa-hat GST (glutathione S-tranferase) glutathione affinity, Calmodulin-binding peptide (CBP), Strep-tag, Cellulose Binding Domain, Maltose Binding Protein, S-Peptide Tag, Chitin Binding Tag, Immunoreactive Epitopes, Epitope Tags, E2Tag, HA Epitope Tag, Myc Epitope, FLAG Epitope, AU1 and AU5 Epitopes, Glu-Glu Epitope, KT3 Epitope, IRS Epitope, Btag Epitope, Protein Kinase-C Epitope, VSV Epitope, lectins that mediate binding to a diversity of compounds, including carbohydrates, lipids and proteins, e.g. Con A (Canavalia ensiformis) or WGA (wheat germ agglutinin) and tetranectin or Protein A or G (antibody affinity).

Preferred Composition: The adjuvant of the composition is selected from saponins such as Quil A and Qs-21, oil in water emulsions such as MF59, MPL, PLG, PLGA, aluminium salts, calcium phosphate, water in oil emulsions such as IFA (Freund's incomplete adjuvant) and CFA (Freund's complete adjuvant), interleukins such as IL-1beta IL-2, IL-7, IL-12, and INFgamma, Adju-Phos (RTM), glucan, antigen formulation, biodegradable microparticles, Cholera Holotoxin, liposomes, DDE, DMEA, DMPC, DMPG, DOC/Alum Complex, ISCOMsr, muramyl **dipeptide**, monophosphoryl lipid A, muramyl tripeptide, and phospatidylethanolamine, preferably from saponins such as Quil A and Qs-21, MF59, MPL, PLG, PLGA, calcium phosphate, and aluminium salts. The excipient is selected from diluents, buffers, suspending agents, wetting agents, solubilizing agents, pH-adjusting agents, dispersing agents, preserving agents, and/or colorants.

Preferred Method: Detecting the presence of MHC recognizing cells in a sample comprises:

(a) providing a sample suspected of comprising MHC recognizing cells;

(b) contacting the sample with a MHC molecule construct; and

(c) determining any binding of the MEC molecule construct, the binding of which indicates the presence of MHC recognizing cells.

Monitoring MHC recognizing cells or establishing a prognosis of a disease or diagnosing a disease, or determining the status of a disease, involving MHC recognizing cells comprises:

(a) providing a sample suspected of comprising MHC recognizing cells;

(b) contacting the sample with a MHC molecule construct; and

(c) determining any binding of the MHC molecule construct.

Determining the effectiveness of a medicament against a disease involving MHC recognizing cells comprises:

(a) providing a sample from a subject receiving treatment with a medicament;

(b) contacting the sample with a MHC molecule construct;

(c) determining any binding of the MHC molecule construct.

The determination of the binding is carried out by inspection in a microscope, by light, by fluorescence, by electron transmission or by flow cytometry. The MHC recognizing cells are selected from subpopulations of CD3+ T-cells, gamma, delta T-cells, alpha, beta T-cells, CD4+ T-cells, T helper cells, CD8+ Tcells, Suppressor T-cells, CD8+ cytotoxic T-cells, cytotoxic T-cells (CTL)s, natural killer (NK) cells, NKT cells, LAK cells, and MAK. The MHC recognizing cells are involved in a disease of inflammatory, auto-immune, allergic, viral, cancerous, infectious, allo- or xenogene (graft versus host and host versus graft) origin. Obtaining MHC recognizing cells comprises:

(a) bringing a sample from a subject comprising MHC recognizing cells into contact with a MHC molecule construct, where the MHC recognizing cells become bound to the MHC molecule construct;

(b) isolating the bound MHC molecule construct and the MHC recognizing

cells; and
(c) expanding the MHC recognizing cells to a clinically relevant number. The isolation is carried out by applying a magnetic field or by flow cytometry. The MHC recognizing cells are liberated from the MHC molecule construct prior to expansion. The disease consists of chronic inflammatory bowel disease such as Crohn's disease or ulcerative colitis, sclerosis, type I diabetes, rheumatoid arthritis, psoriasis, atopic dermatitis, asthma, malignant melanoma, renal carcinoma, breast cancer, lung cancer, cancer of the uterus, cervical cancer, prostate cancer, brain cancer, head and neck cancer, leukemia, cutaneous lymphoma, hepatic carcinoma, colorectal cancer, bladder cancer, rejection-related disease, Graft-versus-host-related disease, or a viral disease associated with hepatitis, acquired immunodeficiency syndrome (AIDS), measles, pox, chicken pox, rubella or herpes. The sample is selected from histological material, cytological material, primary tumors, secondary organ metastasis, fine needle aspirates, spleen tissue, bone marrow specimens, cell smears, exfoliative cytological specimens, touch preparations, oral swabs, laryngeal swabs, vaginal swabs, bronchial lavage, gastric lavage, from the umbilical cord, and from body fluids such as blood (e.g. from a peripheral blood mononuclear cell (PBMC) population isolated from blood or from other blood-derived preparations such as leukopheresis products), from sputum samples, expectorates, and bronchial aspirates. The sample is mounted on a support. An adoptive cellular immunotherapeutic method, inducing energy of a cell, or up-regulating, down-regulating or modulating an immune response in, or treating an animal, including a human being comprises administering the therapeutic composition. Producing a therapeutic composition comprises:
(a) providing the MHC molecule construct solubilizing or dispersing the MHC molecule construct in a medium suitable for therapeutic substances; and
(b) optionally adding other adjuvants and/or excipients.
The method also comprises:
(a) obtaining MHC recognizing cells using the MHC molecule construct;
(b) expanding such MHC recognizing cells to a clinically relevant number,
(c) formulating the obtained cells in a medium suitable for administration; and
(d) optionally adding adjuvants and/or excipients.

L22 ANSWER 7 OF 12 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2002-268905 [31] WPIDS
DNN N2002-209310 DNC C2002-079723
TI Modulated release aerosol formulation useful for treating oral or nasal inhalation-treated diseases such as asthma comprises block copolymer construct comprising selected medicament and a fluid carrier.
DC A96 B05 B07 P32
IN ADJEI, A L; CUTIE, A J; ZHU, Y
PA (AERO-N) AEROPHARM TECHNOLOGY INC
CYC 94
PI WO 2002005785 A1 20020124 (200231)* EN 37
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW
AU 2001081288 A 20020130 (200236)
ADT WO 2002005785 A1 WO 2001-US41129 20010625; AU 2001081288 A AU 2001-81288 20010625
FDT AU 2001081288 A Based on WO 2002005785
PRAI US 2000-702319 20001031; US 2000-219054P 20000718

AB WO 200205785 A UPAB: 20020516
NOVELTY - A modulated release aerosol formulation comprises polymeric construct comprising biodegradable ABA block copolymer comprising selected medicament and a fluid for carrying, and delivering the construct.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for:
(A) preparation of the aerosol formulation comprising
(i) combining the construct with the copolymer to form the polymeric construct;
(ii) combining the construct with the fluid carrier to form a mixture; and
(iii) dispersing the mixture. The medicament is associated with the copolymer to provide effective doses; and
(B) a metered dose inhaler containing the aerosol formulation.
ACTIVITY - Antiasthmatic; Antidiabetic; Cytostatic; Antiallergic; Antiinflammatory; Antianginal.
MECHANISM OF ACTION - None given.
USE - For treating a human being or another animal a condition capable of treatment by oral or nasal inhalation (claimed). For treating conditions e.g. asthma, chronic obstructive pulmonary disease, diabetes, hormone replacement, cancer, erythropoiesis, infection, allergic rhinitis, rhinitis, angina or local infection.
ADVANTAGE - The composition is stable, easily manufactured and effective when administered as fluid dispersed particles to the lung of the patient. The composition provides slow release of the medicament.
Dwg.0/0

TECH UPTX: 20020516
TECHNOLOGY FOCUS - POLYMERS - Preferred Components: The copolymer (preferably in the form of particles) comprises a block segment comprising poly (lactide-co-glycolide) or beta-block segment selected from **polyethylene glycol**, polyethylene oxide, polyoxyethylene, polystyrene, polybutadiene, polyisoprene and/or polyvinyl derivatives. The ABA block copolymer has an average molecular weight of 1000 - 2000 and the beta-block segment is present in an amount of 10 - 60 wt.%
TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Medicament: The medicament comprises a protein or peptide medicament having a molecular size of 1 - 150 k Daltons and is selected form an insulin or its analog, an amylin, an immunodilating protein, an interleukin, an **interferon**, an erythropoietan, heparin, thrombolytic, an antitrypsin, an anti-protease, hormone, growth factor, an enzyme, nucleic acid, an immunoglobulin, an antibiotic, an antiinfective, calcitonin, hematopoietic factor, vaccine, vasoactive peptide, an antisense agent, an oligonucleotide, DNase, cyclosporin and/or ribavirin (preferably LH-RH, deltirex, leuprolide, gosorelin, nafarelin, octreotide, somatostatin, calcitonin, parathyroid hormone, TRH, growth hormone-releasing hormone, G-CSF, G-SF, cytokine, rhDNAse, heparin, an oligonucleotide, ribavarin, glucagon, acetohexamide, chlorpropamide, tolazemide, tolbutamide, glipizide, glyburide, glucophage, phentolamine, tumor neurosis factor (TNF), nerve growth factor (NGF), macrophage-colony stimulating factor (M-CSF), heparinase, bone morphogenic protein (BMP), hANP, glucogon-like peptide (GLP-1)renin, bradykinin, bacitracin, polymyxin, colistin, tyrocidine, gramicidin, monoclonal antibody and/or vaccine, especially troglitazone or rosiglitazone maleate). The troglitazone and rosiglitazone maleate are combined with a second medicament selected from an amylin, insulin and/or an anti-diabetic agent (preferably anti-diabetic agent). The anti-diabetic agent is glucagon, acetohexamide, chlorpropamide, tolazemide, tolbutamide, glipizide, glyburide, glucophage and/or phentolamine.
Preferred Carrier: The fluid carrier is 1,1,1,2-tetragluoethane and/or 1,1,1,2,3,3,3-heptafluoropropane; a compressed gas selected from air, carbon dioxide and/or nitrogen; or a hydrocarbon selected from n-butane,

propane and/or isopentene.
Preferred Composition: The composition further comprises a stabilizer and a cosolvent. The composition is in an aerosol canister equipped with a metered dose value. The stabilizer stabilizes the formation to prevent settling, creasing or flocculation for a time to allow reproducible dosing of the associated medicament after agitation of the formulation. Preferred Method: The method further comprises prior to step (c) combining the mixture with stabilizer.

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Stabilizer: The stabilizer is selected from an amino acid (preferably twenty existing amino acid) and/or its derivatives. The stabilizer can be selected from:
(1) a **dipeptide** selected from a salt and an ester of oxidized and unoxidized L-cysteinylgycine, gamma-L-glutamyl-L-cystcine, N-acetyl-L-cystein-glycine;
(2) a **conjugated**, unconjugated or polymeric form of L-Gly-L-glu and L-Val-L-Thr;
(3) L-aspartyl-L-phenylamine;
(4) a muramyl **dipeptide**;
(5) a nutrient selected from L-tyrosyl-L-tyrosine, L-alanyl-L-tyrosine, L-arginyl-L-tyrosine, L-tyrosyl-L-arginin, N-Clz-L-Liu-OCH and their salts or esters;
(6) glycyl-glycine;
(7) N-acetyl-L-asparate-L-glytamate (NAAG); and/or
(8) a tripeptide selected from an oxidized and an unoxidized form of gamma-L-glutamyl-L-cystcine glycine or a muramyl tripeptide.
The cosolvent is ethanol.

L22 ANSWER 8 OF 12 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2002-179374 [23] WPIDS
DNC C2002-055581
TI Organic solvent-free microspheres for subcutaneous or intramuscular injection, comprising protein drug (e.g. erythropoietin) and prolonged release coating, obtained by coating in supercritical fluid.
DC A18 A96 B04 B07
IN BENOIT, J P; DULIEU, C; RICHARD, J; BENOIT, J
PA (ETHI-N) LAB PROD ETHIQUES ETHYPHARM; (MAIN-N) MAINELAB; (ETHY-N) ETHYPHARM SA; (MAIN-N) MAINELAB SA; (ETHY-N) ETHYPHARM; (BENO-I) BENOIT J; (DULI-I) DULIEU C; (RICH-I) RICHARD J
CYC 97
PI WO 2001089481 A1 20011129 (200223)* FR 31
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
FR 2809309 A1 20011130 (200223)
AU 2001063996 A 20011203 (200225)
NO 2002005552 A 20030120 (200318)
EP 1303259 A1 20030423 (200329) FR
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR
BR 2001011054 A 20030415 (200334)
KR 2003011858 A 20030211 (200339)
HU 2003002012 A2 20030929 (200369)
CN 1438877 A 20030827 (200375)
JP 2003534267 W 20031118 (200401) 27
ZA 2002009553 A 20031126 (200402) 33
US 2004043076 A1 20040304 (200417)

ADT WO 2001089481 A1 WO 2001-FR1575 20010522; FR 2809309 A1 FR 2000-6587 20000523; AU 2001063996 A AU 2001-63996 20010522; NO 2002005552 A WO 2001-FR1575 20010522, NO 2002-5552 20021119; EP 1303259 A1 EP 2001-938300 20010522, WO 2001-FR1575 20010522; BR 2001011054 A BR 2001-11054 20010522, WO 2001-FR1575 20010522; KR 2003011858 A KR 2002-715881 20021123; HU 2003002012 A2 WO 2001-FR1575 20010522, HU 2003-2012 20010522; CN 1438877 A CN 2001-809902 20010522; JP 2003534267 W JP 2001-585726 20010522, WO 2001-FR1575 20010522; ZA 2002009553 A ZA 2002-9553 20021125; US 2004043076 A1 WO 2001-FR1575 20010522, US 2003-296314 20030527

FDT AU 2001063996 A Based on WO 2001089481; EP 1303259 A1 Based on WO 2001089481; BR 2001011054 A Based on WO 2001089481; HU 2003002012 A2 Based on WO 2001089481; JP 2003534267 W Based on WO 2001089481

PRAI FR 2000-6587 20000523

AB WO 200189481 A UPAB: 20020411

NOVELTY - Novel microspheres (A) for administration by subcutaneous or intramuscular injection, comprising a protein active agent (I) and a coating (II) providing prolonged release, are obtained by stirring a mixture of (I) and (II) in a supercritical fluid (III) in which (II) is soluble, so that the obtained (A) are completely free of organic solvents and (I) is not denatured.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for the preparation of (A) by suspending and dissolving (I) and (II) respectively in (III) and adjusting the temperature and/or pressure under continuous stirring so that (II) is desolubilized in controlled manner and coacervated onto (I).

USE - (A) are useful for administration of a wide range of protein drugs (I) for prolonged release, by subcutaneous or intramuscular injection. (I) is typically erythropoietin for treating anemia, during hemodialysis of chronic renal insufficiency patients receiving hemodialysis, associated with chemotherapy, in HIV patients or before surgery; or **interferon**- alpha for antiviral, anticancer or immunomodulatory therapy, e.g. of hepatitis B or C, leukemia or Kaposi sarcoma

ADVANTAGE - (A) are totally free of all traces of (potentially harmful) organic solvents. Even highly heat-sensitive (I) are not denatured and retain their biological activity. (A) have an advantageous matrix structure and are obtained by a simple procedure.

Dwg.0/5

TECH UPTX: 20020411

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Active Agents: (I) is parathyroid hormone related peptide, growth hormone, **interferon** -alpha, -beta or -gamma, erythropoietin-alpha or -beta, granulocyte colony stimulating factor, granulocyte macrophage colony stimulating factor, pituitary adenylate cyclase activating polypeptide, vasoactive intestinal peptide, thyrotropin releasing hormone, corticotropin releasing hormone, arginine vasopressin, angiotensin, insulin, somatotropin, hepatitis B viral antigen HBS, tissue plasminogen activator, coagulation factor VIII or IX, glucosyl ceramidase, sargramostim, lenograstin, filgrastin, interleukin-2, domase-alpha, molgramosim, **PEG**-L-saparaginase, **PEG**-adenosine deaminase, hirudin, eptacog-alpha (human blood coagulation factor VIIa) nerve growth factor (NGF, CNTF, BDNG, FGF or GDNF); or a derivative of luteinizing hormone releasing hormone (LHRH) or somatastin, triptorelin, bombesin, calcitonin, parathyroid hormone, gastrin releasing peptide, LHRH, growth hormone releasing factor, derivatives of Acetyl-Ser-**Asp**-Lys-**Pro** or amylin.

Erythropoietin is especially preferred. Preferred Microspheres: (A) have average particle size 0.1-150 mum, and contain (I) at 0.5-50 (preferably 3-20) wt. %.

(II) are:

(i) polymers selected from biodegradable (co)polymers of

alpha-hydroxycarboxylic acids (specifically (co)polymers of lactic or glycolic acid, especially poly-L-lactide or polylactic-co-glycolic acid), poly-(epsilon-caprolactone) or its derivatives, poly-(beta-hydroxybutyrate), poly-(hydroxyvalerate), (beta-hydroxybutyrate-hydroxyvalerate) copolymers, polymalic acid, amphiphilic polylactic acid-polyethylene oxide block copolymers, biocompatible **polyethylene glycols**, polyethylene oxide, polyethylene oxide-polypropylene oxide copolymers, polyanhydrides, polyorthoesters and/or polyphosphazenes; or
(ii) lipids such as phospholipids (specifically phosphatidyl choline, phosphatidyl glycerol, diphosphatidyl glycerol, dipalmitoyl phosphatidyl choline, dioleyl phosphatidyl ethanolamine, dioleyl phosphatidyl choline or dimyristoyl phosphatidyl glycerol), 10-18C fatty acid glycerides, mono-, di- or triglycerides (specifically 8-12C triglycerides such as capric-caprylic, myristic, palmitic or stearic triglycerides) and/or solid fatty acid esters (specifically esters of 8-18C (especially 8-12C) acids such as ethyl palmitate, ethyl myristate or octyl-dodecyl myristate), particularly Gelucire (RTM; mixture of mono-, di- and triglycerides, fatty acid esters and **polyethylene glycol**).
Preferred Process: The concentration of (II) in (III) is 1.5-4.5 (especially ca. 2) g/l. Coacervation is carried out at 30-45 degrees C under a pressure of 100-280 x 10 to power 5 (especially 180-220 x 10 to power 5) Pa, with stirring at 100-1000 (especially 450) rpm. An insert (preferably formed from two sintered parts allowing entry of (III)) is placed in the autoclave, and the suspending of (I) and dissolution of (II) are carried out in the autoclave.

TECHNOLOGY FOCUS - POLYMERS - Preferred Materials: (II) include polymers selected from biodegradable (co)polymers of alpha-hydroxycarboxylic acids (specifically (co)polymers of lactic or glycolic acid, especially poly-L-lactide or polylactic-co-glycolic acid), poly-(epsilon-caprolactone) or its derivatives, poly-(beta-hydroxybutyrate), poly-(hydroxyvalerate), (beta-hydroxybutyrate-hydroxyvalerate) copolymers, polymalic acid, amphiphilic polylactic acid-polyethylene oxide block copolymers, biocompatible **polyethylene glycols**, polyethylene oxide, polyethylene oxide-polypropylene oxide copolymers, polyanhydrides, polyorthoesters and/or polyphosphazenes.

L22 ANSWER 9 OF 12 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2002-075125 [10] WPIDS
DNC C2002-095564
TI A medicinal aerosol formulation comprising troglitazone, a fluid carrier , a stabilizer and optionally a further active agent used to treat e.g. asthma, diabetes, rhinitis, angina, local infection etc..
DC B05 D16
IN ADJEI, A L; CUTIE, A J
PA (AERO-N) AEROPHARM TECHNOLOGY INC
CYC 95
PI WO 2001082868 A2 20011108 (200210)* EN 16
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW
AU 2001059318 A 20011112 (200222)
US 6464959 B1 20021015 (200271)
ADT WO 2001082868 A2 WO 2001-US14043 20010501; AU 2001059318 A AU 2001-59318 20010501; US 6464959 B1 Provisional US 2000-201248P 20000501, US 2000-702779 20001031

FDT AU 2001059318 A Based on WO 2001082868
PRAI US 2000-702779 20001031; US 2000-201248P 20000501
AB WO 200182868 A UPAB: 20020613
NOVELTY - A medicinal aerosol formulation comprises troglitazone or its derivative, a fluid carrier and a stabilizer selected from an amino acid or its derivative, or their mixture.
DETAILED DESCRIPTION - An INDEPENDENT CLAIM is made for a metered dose inhaler containing a medicinal aerosol formulation comprising troglitazone or its derivative, a fluid carrier and a stabilizer selected from an amino acid its derivative, or their mixture.
ACTIVITY - Bronchodilatory; Antiasthmatic; Antiallergic; Antiinflammatory; Antidiabetic; antianginal; Anti-infective.
MECHANISM OF ACTION - None given.
USE - The formulation is used to effect bronchodilation or to treat a condition susceptible of treatment by inhalation e.g. asthma, chronic obstructive pulmonary disease, allergic rhinitis, rhinitis (local) , diabetes, angina or local infection.
ADVANTAGE - A stable aerosol formulation is obtained without the use of either cosolvents or surfactants.
Dwg.0/0
TECH UPTX: 20020613
TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Active Agent: The troglitazone is preferably in the form of the maleate. A second medicament is optionally present and is selected from insulin, an insulin analog, an amylin, an immunomodulating protein, an interleukin, an **interferon** , an erythropoeitin, a heparin, a thrombolytic, an antitrypsin, an anti-protease, a hormone, a growth factor, an enzyme, a nucleic acid, an immunoglobulin, an antibiotic, an antiinfective, a calcitonin, a hematopoietic factor, a vaccine, a vasoactive peptide, an antisense agent, an oligonucleotide, DNAase, a cyclosporin, and/or ribavirin. More specifically it may be glucagon, octreotide, somatostatin, IgG, IgE, IgM, IgA, IgD, a gene, a vector, glucagon, acetohexamide, chlorpropamide, tolazemide, tolbutamide, glipizide, glyburide, glucophage or phentolamine.
Preferred Stabilizer: The stabilizer is selected from the group consisting of the existing twenty amino acids, a mixture and or derivative e.g a **di-peptide** selected from a salt and an ester of oxidized and unoxidized L-cysteinylglycine, gamma-L-glutamyl-L-cysteine, N-acetyl-L-cysteine glycine; a **conjugated**, unconjugated or **polymeric** form of L-Gly-L-Glu and L-Val-L-Thr; L-aspartyl-L-phenylalanine; a muramyl **dipeptide**; a nutrient selected from l-tyrosyl-L-tyrosine, L-alanyl-L-tyrosine, L-arginyl-L-tyrosine, L-tyrosyl-L-arginine, N-Cbz-L-Leu-L-Leu-OCH and salts and esters thereof; glycyl-glycine; N-acetyl-L-aspartate-L-glutamate; a tripeptide selected from an oxidized or unoxidized form of gamma-L-glutamyl-L-cysteinylglycine or a muramyl tripeptide; or a mixture of any of the above stabilizers. The stabilizer is present in an amount 0.001 to about 200,000 parts per million of the total weight of the formulation.
Preferred Fluid Carrier: The carrier is a propellant selected from 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3,-heptafluoropropane or mixture or a hydrocarbon propellant selected n-butane, propane, isopentane or mixture.
Preferred Formulation: the formulation may optionally further comprise a cosolvent e.g. ethanol.
Preferred Metered Dose Inhaler: The formulation is in an aerosol canister with a metered dose valve.

L22 ANSWER 10 OF 12 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2002-062072 [08] WPIDS
DNC C2002-017692

TI Aerosol compositions useful for treating diabetes contain pioglitazone maleate and are free of surfactants and co-solvents.
DC B03
IN ADJEI, A L; CUTIE, A J; SEXTON, F A
PA (AERO-N) AEROPHARM TECHNOLOGY INC
CYC 95
PI WO 2001082873 A2 20011108 (200208)* EN 16
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW
AU 2001026234 A 20011112 (200222)
EP 1307243 A2 20030507 (200332) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR
US 6610272 B1 20030826 (200357)
JP 2003531842 W 20031028 (200373) 22
ADT WO 2001082873 A2 WO 2001-US34 20010102; AU 2001026234 A AU 2001-26234 20010102; EP 1307243 A2 EP 2001-900816 20010102, WO 2001-US34 20010102; US 6610272 B1 Provisional US 2000-201232P 20000501, US 2000-718039 20001120; JP 2003531842 W JP 2001-579749 20010102, WO 2001-US34 20010102
FDT AU 2001026234 A Based on WO 2001082873; EP 1307243 A2 Based on WO 2001082873; JP 2003531842 W Based on WO 2001082873
PRAI US 2000-718039 20001120; US 2000-201232P 20000501
AB WO 200182873 A UPAB: 20020204
NOVELTY - Surfactant and co-solvent free aerosol compositions containing pioglitazone maleate, useful for treating diabetes, are new.
DETAILED DESCRIPTION - A medicinal aerosol comprises pioglitazone maleate, an amino acid type stabilizer and a fluid carrier.
ACTIVITY - Antidiabetic.
MECHANISM OF ACTION - Not stated.
USE - Useful for treating diabetes and diabetes-related conditions.
ADVANTAGE - The use of surfactants and co-solvents are not required for a stable composition as per existing formulations.
Dwg.0/0
TECH UPTX: 20020204
TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Composition: Preferred composition contains pioglitazone maleate (1-500mg), an optional second medication selected from glucagon, acetohexamide, chlorpropamide, tolazemide, tolbutamide, glipizide, glyburide, glucophage, phentolamine, an amylin, in interleukin, an **interferon**, an erythropoietin, a heparin, a thrombolytic, an antitrypsin, an anti-protease, a hormone, an growth factor, an enzyme, a nucleic acid, an immunoglobulin, an antibiotic, an anti-infective, a calcitonin, a hemopoietic factor, an immunomodulating protein, a vaccine, a vasoactive peptide, an antisense agent, an oligonucleotide, a gene, a vector, a DNase, a cyclosporin, a ribavirin, an insulin (or a mix). The stabilizer (0.001-200,000 parts per million by weight) is any amino acid or mixture thereof including **dipeptides** selected from salts or esters of oxidized and unoxidized L-cysteinylglycine, gamma-L-glutamyl-L-cysteine, N-acetyl-L-cysteine-glycine; optionally **conjugated** or **polymeric** forms of L-Gly-L-Glu or L-Val-L-Thr; L-aspartyl-L-phenylalanine; a muramyl **dipeptide**; a nutrient (including salts or esters) selected from L-tyrosyl-, L-alanyl-, L-arginyl-L-tyrosine, L-tyrosinyl-L-arginine, N-Cbz-L-Leu-L-Leu-OCH; glycyl glycine; N-acetyl-L-aspartate-L-glutamate; tripeptides selected from optionally oxidized gamma-L-glutamyl-L-cysteinylglycine or a muramyl tripeptide (or a mix of any stabilizers). The fluid carrier is

1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3 heptafluoropropane, n-butane, propane, isopentane (or a mix) , compressed air, carbon dioxide or nitrogen (or a mix). Water is used as an optional stabilizer (10-5000 parts per million by weight). The preferred optional co-solvent is ethanol. The aerosol dose is optionally metered.

L22 ANSWER 11 OF 12 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2001-596689 [67] WPIDS
CR 2001-557522 [62]
DNN N2001-444889 DNC C2001-176515
TI Formulation to treat e.g. asthma comprises a protein or peptide medicament in a fluid carrier and a stabilizer selected from an amino acid or its derivative.
DC B04 D16 P34
IN ADJEI, A L; STEFANOS, S; SUN, J Z; ZHU, Y
PA (AERO-N) AEROPHARM TECHNOLOGY INC
CYC 94
PI WO 2001060420 A1 20010823 (200167)* EN 26
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW
AU 2001027559 A 20010827 (200176)
EP 1292283 A1 20030319 (200322) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR
JP 2003524646 W 20030819 (200356) 30
MX 2002007187 A1 20021201 (200377)
CN 1440298 A 20030903 (200380)
ADT WO 2001060420 A1 WO 2001-US117 20010102; AU 2001027559 A AU 2001-27559 20010102; EP 1292283 A1 EP 2001-901681 20010102, WO 2001-US117 20010102; JP 2003524646 W JP 2001-559515 20010102, WO 2001-US117 20010102; MX 2002007187 A1 WO 2001-US117 20010102, MX 2002-7187 20020724; CN 1440298 A CN 2001-807195 20010102
FDT AU 2001027559 A Based on WO 2001060420; EP 1292283 A1 Based on WO 2001060420; JP 2003524646 W Based on WO 2001060420; MX 2002007187 A1 Based on WO 2001060420
PRAI US 2000-702195 20001030; US 2000-177982P 20000125; US 2000-177987P 20000125
AB WO 200160420 A UPAB: 20031211
NOVELTY - Medicinal formulation comprises (a) a protein or peptide medicament having about 1 - 150 K Dalton molecular size, (b) a fluid carrier for containing (a) and (c) a stabilizer selected from amino acid(s) and/or derivative(s).

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following:

(1) preparing a stable medicinal aerosol formulation which comprises combining (a), (b) and (c) and dispersing them (preferably using cosolvent in both steps);

(2) a formulation which is in an aerosol canister equipped with a metered dose valve;

(3) a method of stabilizing a suspension aerosol formulation comprising a propellant and a protein or peptide medicament which comprises incorporating a stabilizer to prevent settling, creaming, or flocculation of the formulation; and

(4) a metered dose inhaler which contains a medicinal aerosol formulation comprising (a), propellant and (c).

ACTIVITY - Antiallergic; Antiinflammatory; Antiasthmatic;

Antidiabetic; Antianginal.

MECHANISM OF ACTION - None given.

USE - To effect bronchodilation in a human or an animal or to treat a condition e.g. asthma, chronic obstructive pulmonary disease, allergic rhinitis, rhinitis, diabetes, angina or local infection, cystic fibrosis, pneumonia, pain management immune deficiency, hormonal therapy and erythropoiesis.

ADVANTAGE - There is no settling, creaming or flocculation of the medicine and it is reproducible (claimed). The medicine is stable and does not require cosolvents or surfactants.

Dwg.0/0

TECH UPTX: 20011119

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Medicament: The medicament is selected from an insulin, an insulin analog, an amylin, an immunomodulating protein, an interleukin, an **interferon**, an erythropoietin, a heparin, a thrombolytic, an antitrypsin, an anti-protease, a hormone, a growth factor, an enzyme, a nucleic acid, an immunoglobulin, an antibiotic, an antiinfective, a calcitonin, a hematopoietic factor, a vaccine, a vasoactive peptide, an antisense agent, an oligonucleotide, Dnase, a cyclosporin and/or ribavirin (preferably an insulin, an insulin analog, an amylin, glucagon, LH-RH, deltirex, leuprolide, gosorelin, nafarelin, octreotide, somatostatin, a calcitonin, parathyroid hormone, TRH, growth hormone-releasing hormone, G-CSF, G-SF, a cytokine, rhDNAse, a heparin, an antibiotic, albumin, ovalbumin, aminloride, DDAVP, VIP, a cyclosporin, an erythropoietin, an **interferon**, IgG, IgE, IgM, IgA, IgD, an interleukin, IRAP, papain, peroxidase, serratio peptidase, catalase, alpha-1-antitrypsin, a gene; a vector, an amiloride, a rhDNAse, an oligonucleotide and/or ribavirin). Preferred Stabilizer: The stabilizer is selected from any mixture of twenty amino acids or their derivatives (preferably a **di-peptide** selected from a salt and an ester of oxidized and unoxidized L-cysteinylglycine, gamma-L-glutamyl-L-cysteine, N-acetyl-L-cysteine-glycine; a **conjugated**, unconjugated or **polymeric** form of L-Gly-L-Glu and L-Val-L-Thr; L-aspartyl-L-phenylalanine; a muramyl **dipeptide**; a nutrient selected from L-tyrosyl-L-tyrosine, L-alanyl-L-tyrosine, L-arginyl-L-tyrosine, L-tyrosyl-L-arginine, N-Cbz-L-Leu-L-Leu-OCH and their salts or esters; glycyl-glycine; N-acetyl-L-aspartate-L-glutamate and/or a tripeptide selected from an oxidized and an unoxidized form of gamma-L-glutamyl-L-cysteinylglycine or a muramyl tripeptide. Preferred Fluid Carrier: The carrier is a propellant selected from 1,1,1,2-tetrafluoroethane and/or 1,1,1,2,3,3,3-heptafluoropropane (preferably a hydrocarbon propellant selected from n-butane, propane and/or isopentane). Preferred Formulation: The formulation further includes a cosolvent (preferably comprises ethanol). The stabilizer is present to prevent settling, creaming or flocculation of the formulation to allow reproducible dosing of the drug after agitation of the formulation (preferably about 0.001 - 200,000 parts per million of the total weight of the formulation).

L22 ANSWER 12 OF 12 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2000-681105 [67] WPIDS
DNC C2000-207282
TI Compositions to deliver compounds into cells e.g. to treat rheumatoid arthritis, comprise organic halide, targeting ligand and nuclear localization sequence in combination with compound and carrier.
DC A96 B07 D16
IN MCCREERY, T; SADEWASSER, D A; UNGER, E C
PA (IMAR-N) IMARX PHARM CORP
CYC 25

PI EP 1046394 A2 20001025 (200067)* EN 78
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI
ADT EP 1046394 A2 EP 2000-303249 20000418
PRAI US 1999-294623 19990419
AB EP 1046394 A UPAB: 20001223
NOVELTY - Compositions for delivering compounds into cells comprise: an organic halide; a targeting ligand; and a nuclear localization sequence in combination with the compound to be delivered.

ACTIVITY - Immunoregulatory; anti-inflammatory; anti-arthritic.

USE - The compositions are used to deliver compounds into cells (claimed), particularly for the treatment of autoimmune disorders and inflammatory conditions such as rheumatoid arthritis. They may also be used to deliver pharmaceuticals, drugs, diagnostic agents, synthetic organic molecules, peptides, proteins, vitamins, steroids, genetic materials and other bioactive agents e.g. mitotic inhibitors (vinca alkaloids), radiopharmaceuticals (radioactive iodine, phosphorus and cobalt isotopes), hormones (progestins, estrogens, anti-estrogens), anthelmintics, antimalarials, antituberculotics, biologicals (immune sera, antitoxins, antivenoms), rabies prophylactic products, bacterial vaccines, viral vaccines, aminoglycosides, respiratory products (xanthine derivatives, theophylline, aminophylline), thyroid therapeutics (iodine salts, antithyroid agents), cardiovascular products (chelating agents, mercurial diuretics, cardiac glycosides), glucagons, blood products (parenteral iron, hemin, hematoporphyrins and derivatives), targeting ligands (peptides, antibodies, antibody fragments), biological response modifiers (muramyl **dipeptide**, muramyl tripeptide, microbial cell wall components, lymphokines - bacterial endotoxin e.g. lipopolysaccharide and macrophage activation factor), subunits of bacteria (Mycobacteria, Comebacteria), synthetic **dipeptides** (N-acetyl-muramyl-L-alanyl-D-isoglutamine), antifungals (ketoconazole, nystatin, griseofulvin, flucytosine, miconazole, amphotericin B), toxins (ricin), immunosuppressants (cyclosporins), antibiotics (beta -lactam, sulfazecin), hormones (growth hormone, melanocyte-stimulating hormone, estradiol, beclomethasone dipropionate, betamethasone, betamethasone acetate, betamethasone sodium phosphate, betamethasone disodium phosphate, cortisone acetate, dexamethasone, dexamethasone acetate, dexamethasone sodium phosphate, flunisolide, hydrocortisone, hydrocortisone acetate, hydrocortisone cypionate, hydrocortisone sodium phosphate, hydrocortisone sodium succinate, methylprednisolone, methylprednisolone acetate, methylprednisolone sodium succinate, paramethasone acetate, prednisolone acetate, prednisolone sodium phosphate, prednisolone tebutate, prednisone, triamcinolone, triamcinolone acetonide, triamcinolone diacetate, triamcinolone hexacetonide, fluorocortisone acetate, oxytocin, vasopressin and their derivatives), vitamins (cyanocobalamin neionic acid), retinoids and their derivatives (retinal palmitate, alpha -tocopheryl), peptides and enzymes (manganese superoxide dismutase, alkaline phosphatases), anti-allergens (amelexanox), anticoagulants (phenprocoumon, heparin), tissue plasminogen activators, streptokinase and urokinase), circulatory drugs (propranolol), metabolic potentiators (glutathione), antibiotics (p-aminosalicylic acid, isoniazid, capreomycin sulfate, cycloserine, ethambutol hydrochloride, ethionamide, pyrazinamide, rifampicin, streptomycin sulfate dapsone, chloramphenicol, neomycin, ceflacor, cefadroxil, cephalexin, cephadrine erythromycin, clindamycin, lincomycin, amoxicillin, ampicillin, bacampicillin, carbenicillin, dicloxicillin, cyclacillin, picloxicillin, hetacillin, methicillin, nafcillin, oxacillin, penicillin (G and V), ticarcillin, rifampin, tetracycline), antivirals (acyclovir, ddI, foscarnet, zidovudine, ribavirin, vidarabine monohydrate), antianginals (diltiazem, nifedipine, verapamil, erythritol tetranitrate, isosorbide dinitrate, nitroglycerin (glyceryl trinitrate),

pentaerythritol tetranitrate, anti-inflammatories (difluisal, ibuprofen, indomethacin, meclofenamate, mefenamic acid, naproxen, oxyphenbutazone, phenylbutazone, piroxicam, sulindac, tolmetin, aspirin, salicylates), antiprotozoans (chloraquine, hydroxychloraquine, metronidazole, quinine, meglumine antimonate), antirheumatics (penicillamine), narcotics (paregoric), opiates (codeine, heroin, methadone, morphine, opium), cardiac glycosides (deslanoside, digitoxin, digoxin, digitalin, digitalis), neuromuscular blockers (atracurium mesylate, gallamine triethiodide, hexafluorenium bromide, metrocurine iodide, pancurium bromide, succinylcholine chloride (suxamethionium chloride), tubocurarine chloride, vencuronium bromide), sedatives (amobarbital, amobarbital sodium, aprobarbital, butabarbital sodium, chloral hydrate, ethchlorvynol, ethinamate, flurazepam hydrochloride, glutethimide, methotrimeprazine hydrochloride, methyprylon, midazolam hydrochloride, paraldehyde, pentobarbital, pentobarbital sodium, secobarbital sodium, thiopental sodium), antineoplastics (methotrexate, fluorouracil, adriamycin, mitomycin, ansamitomycin, bleomycin, cysteine arabinoside, arabinosyl adenine, mercaptopolylysine, vincristine, busulfan, chlorambucil, azidothymidine, melphalan (e.g. PAM, L-PAM or phenylalanine mustard), mercaptopurine, mitotane, procarbazine hydrochloride, dactinomycin (actinomycin D), daunorubicin hydrochloride, dosorubicin hydrochloride, Taxol (RTM: paclitaxel), plicamycin (mithramycin), aminoglutethimide, estramustine phosphate sodium, flutamide, leuprolide acetate, megestrol acetate, tamoxifen citrate, testolactone, trilostane, amsacrine (m-AMSA), asparaginase, etoposide (VP-16), **interferon** alpha -2a, **interferon** alpha -2b, teniposide (VM-26), vinblastine sulfate (VLB), vincristine sulfate, hydroxyurea, procarbaxine or dacarbazine).

ADVANTAGE - The compositions provide improved delivery of compositions including drugs and genetic materials into cells. They provide for specific targeting and delivery of compounds to particular cells and increased targeting to the nuclei of targeted cells. They also allow delivery to cell lines that would be otherwise resistant to intracellular delivery and gene expression using other conventional means.

DESCRIPTION OF DRAWING(S) - Schematic representation of a targeted composition.

targeted composition 1
lipid coating 2
lipids 2A
halocarbon gas or liquid 3
genetic material 4
targeting ligand 5
lipid head group 6
tether 7
tether 7A
nuclear localization sequence 8
condensing agent. 9
Dwg.2/2

TECH UPTX: 20001223

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred organic halide - The organic halide is a gaseous or liquid organic halide, preferably a liquid or a gaseous precursor. The organic halide is a fluorinated compound, preferably a perfluorinated compound, more preferably a perfluorocarbon, especially a perfluoroether compound. The organic halide is 1-bromo-nonafluorobutane, perfluorooctyliodide, perfluorooctylbromide, 1-chloro-1-fluoro-1-bromomethane, 1,1,1-trichloro-2,2,2-trifluoroethane, 1,2-dichloro-2,2-difluoroethane, 1,1-dichloro-1,2-difluoroethane, 1,2-dichloro-1,1,3-trifluoropropane, 1-bromoperfluorobutane, 1-bromo-2,4-difluorobenzene, 2-iodo-1,1,1-trifluoroethane, 5-bromovalerylchloride, 1,3-dichlorotetrafluoroacetone, bromine pentafluoride, 1-bromo-1,1,2,3,3,3-hexafluoropropane, 2-chloro-1,1,1,4,4,4-

hexafluoro-2-butene, 2-chloropentafluoro-1,3-butadiene, iodotrifluoroethylene, 1,1,2-trifluoro-2-chloroethane, 1,2-difluorochloroethane, 1,1-difluoro-2-chloroethane, 1,1-dichlorodifluoromethane, dibromofluoromethane, chloropentafluoroethane, bromochlorodifluoromethane, dichloro-1,1,2,2-tetrafluoroethane, 1,1,1,3,3-pentafluoropentane, perfluorotributylamine, perfluorotripropylamine, 3-fluorobenzaldehyde, 2-fluoro-5-nitrotoluene, 3-fluorostyrene, 3,5-difluoroaniline, 2,2,2-trifluoroethylacrylate, 3-(trifluoromethoxy)-acetophenone, 1,2,2,3,3,4,4-octafluorobutane, 1,1,1,3,3-pentafluorobutane, 1-fluorobutane, 1,1,2,2,3,3,4,4-octafluorobutane, 1,1,1,3,3-pentafluorobutane, perfluoro-4-methylquinolizidine, perfluoro-N-methyl-decahydroquinone, perfluoro-N-methyl-decahydroisoquinone, perfluoro-N-cyclohexyl-pyrrolidine, perfluoroheptane, perfluorocyclohexane, perfluoromethane (preferred), perfluoroethane (preferred), perfluoropropane (preferred), perfluorobutane (preferred), perfluoropentane (preferred), perfluorohexane (preferred), perfluoroheptane (preferred), perfluorooctane (preferred), perfluorononane (preferred), perfluorodecane (preferred), perfluorododecane (preferred), perfluoro-2-methyl-2-pentene (preferred), perfluorocyclohexane (preferred), perfluorodecalin (preferred), perfluorododecalin (preferred), perfluoropropylene, perfluorocyclobutane, perfluoro-2-butyne, perfluoro-2-butene, perfluorobuta-1,3-diene, perfluorobutylethyl ether (preferred), bis(perfluoroisopropyl)ether (preferred), bis(perfluoropropyl)ether (preferred), perfluorotetrahydropyran (preferred), perfluoromethyl tetrahydrofuran (preferred), perfluoro-tertiary butyl-methyl ether (preferred), perfluoro-isobutyl-methyl ether (preferred), perfluoro-n-butyl-methyl ether, perfluoro-isopropyl-methyl ether (preferred), perfluoro-n-propyl-methyl ether (preferred), perfluorodiethyl ether (preferred), perfluorocyclopropyl methyl ether (preferred), perfluoromethyl ethyl ether (preferred), perfluorodimethyl ether (preferred), sulfur hexafluoride or selenium hexafluoride.

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred compositions - The compositions further comprises a carrier such as a polymer, lipid, protein or metal ion. The carrier preferably comprises a lipid, more preferably a cationic lipid, especially N-(1-(2,3-dioleoyloxy)propyl)-N,N,N-trimethylammonium chloride. The carrier preferably comprises a polymer, more preferably a polyethylene, polyoxyethylene, polypropylene, pluronic acid or alcohol, polyvinyl, polyvinylpyrrolidone, arabinan, fructan, fucan, galactan, galacturonan, glucan, mannan, xylan, levan, fucoidan, carrageenan, galactocarolose, pectin, pectic acid, amylose, pullulan, glycogen, amylopectin, cellulose, carboxylmethylcellulose, hydroxypropylmethylcellulose, dextran, pustulan, chitin, agarose, keratan, chondroitin, dermatan, hyaluronic acid, alginic acid, homopolymer or heteropolymer containing one or more of an aldose, ketose, acid, amine, erythrose, threose, ribose, arabinose, xylose, lyxose, allose, altrose, glucose, mannose, gulose, idose, galactose, talose, erythrulose, ribulose, xylulose, psicose, fructose, sorbose, tagatose, glucuronic acid, gluconic acid, glucaric acid, galacturonic acid, mannuronic acid, guluronic acid, glucosamine, galactosamine or neuraminic acid. The carrier is Lipofectin, Lipofectamine, Transfectace, Transfectam, Cytofectin, dimyristoyloxypropyl-3-dimethylhydroxyethylammonium bromide (DMRIE), dilauryloxypropyl-3-dimethylhydroxyethylammonium bromide (DLRIE), GAP-DLRIE, 1,2-dioleoyloxy-3-(trimethylammonio)propane (DOTAP), dioleoylphosphatidylethanolamine (DOPE), DMEAP, DODMP, dioleoylphosphtadiylcholine (DOPC), DDAB, 2,3-dioleoyloxy-N-(2-(sperminecarboxamidoethyl)-N,N-dimethyl-1-propanaminium trifluoroacetate (DOSPA), EDLPC, EDMPC, DPH, TMADPH, cetyltrimethylammonium bromide (CTAB), lysyl-PE, 3,beta-(N,(N',N'-dimethylaminoethane)carbamoyl)cholesterol (DC-Chol), alanyl cholesterol, DCGS, dipalmitoylphosphatidylethanolamine-5-

carboxyspermylamide (DPPES), dicaproylphosphatidylethanolamine (DC PE), 4-dimethylaminopyridine (DMAP), dimyristoylphosphatidylethanolamine (DMPE), dioctadecylamidoglycol spermidine (DOGS), DOFIME, dipalmiotylethylphosphatidylcholine (DPEPC), Pluronic (RTM: **polyethylene glycol**), Tween (RTM: polysorbate), Brij (RTM: polyoxyethylene glycol), plasmalogen, phosphatidylethanolamine, phosphatidylcholine, glycerol-3-ethylphosphatidylcholine, dimethylammonium propane, trimethylammonium propane, dimethyldioctadecylammonium bromide, sphingolipids, sphingomyelin, lysolipid, glycolipid, sulfatide, glycosphingolipid, cholesterol, cholesterol ester, cholesterol salt, oil, 1,2-dioleoyl-sn-glycerol, N-succinyldioleoylphosphatidylethanolamine, 1,3-dipalmitoyl-2-succinyl-glycerol, 1,2-dipalmitoyl-sn-3-succinylglycerol, palmitoylhomocysteine, 1-hexadecyl-2-palmitoylglycerophosphatidylethanolamine, N,N''-bis(dodecylaminocarbonylmethylene)-N,N'-bis((N,N,N-trimethylammoniumethylaminocarbonylethylene)ethylene diamine tetraiodide, N,N''-bis(hexad ecylaminocarbonylmethylene)-N,N,N''-tris-N,N,N-trimethylammoniumethylaminocarbonylmethylenediethylenetriamine hexaiodide, N,N'-bis(dodecylaminocarbonylmethylene)-N,N''-bis((N,N,N-trimethylammoniumethylaminocarbonyl-methylene)-cyclohexylene-1,4-diamine-tetraiodide, 1,1,7,7-tetra((N,N,N-tetramethylammoniumethylaminocarbonylmethylene)-3-hexadecylaminocarbonylmethylene-1,3,7-triaazaheptane heptaiodide or N,N,N',N'-tetra-((N,N,N-trimethylammoniumethylaminocarbonylmethylene)-N'-(1,2-dioleoylglycero-3-phosphoethanolaminocarbonylmethylene) diethylene triamine tetraiodide. The carrier comprises a dioleoylphosphatidylethanolamine, fatty acid, lysolipid, phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, phosphatidylglycerol, phosphatidylinositol, sphingolipid, glycolipid, glucolipid, sulfatide, glycosphingolipid, phosphatidic acid, palmitic acid, stearic acid, arachidonic acid, oleic acid, lipid bearing a polymer, lipid bearing a sulfonated saccharide, cholesterol, tocopherol hemisuccinate, lipid with an ether-linked fatty acid, lipid with an ester-linked fatty acid, polymerized lipid, diacetyl phosphate, stearylamine, cardiolipin, phospholipid with a fatty acid of 6-8C, phospholipid with asymmetric acyl chains, 6-(5-cholesten-3b-yloxy)-1-thio-b-D-galactopyranoside, digalactosyldiglyceride, 6-(5-cholesten-3beta-yloxy)hexyl-6-amino-6-deoxy-1-thio-b-D-galactopyranoside, 6-(5-cholesten-3b)-yloxy)hexyl-6-amino-6-deoxyl-1-thio-alpha-D-mannopyranoside, 12-(((7'-diethylamino-coumarin-3-yl)carbonyl)methylamino)octadecanoic acid, N-(12-(((7'-diethylamino-coumarin-3-yl)carbonyl)methylamino)octadecanoyl)-2-aminopalmitic acid, cholesteryl (4'-trimethyl-ammonio)butanoate, N-succinyldioleoylphosphatidylethanolamine, 1,2-dioleoyl-sn-glycerol, 1,2-dipalmitoyl-sn-3-succinyl-glycerol, 1,3-dipalmitoyl-2-succinylglycerol, 1-hexadecyl-2-palmitoylglycerophosphoethanolamine and/or palmitoylhomocysteine. The carrier comprises a phosphatidylcholine, preferably dioleoylphosphatidylcholi ne, dimyristoylphosphatidylcholine, dipentadecanoylphosphatidylcholine, dilauroylphosphatidylcholine, dipalmitoylphosphatidylcholine or distearoylphosphatidylcholine. The carrier comprises phosphatidylethanolamine, preferably dioleoylphosphatidylethanolamine. The carrier comprises a glycolipid, preferably ganglioside GM1 or GM2. The carrier comprises a lipid bearing a polymer, preferably **polyethylene glycol**, chitin, hyaluronic acid or polyvinylpyrrolidone, more preferably **polyethylene glycol**, especially a **polyethylene glycol** with a molecular weight of 2,000, 5,000 or 8,000. The carrier comprises a phospholipid with asymmetric acyl chains with one acyl chain of about 6 C in length and another of about 12 C in length. The carrier comprises about 82 mole % dipalmitoylphosphatidylcholine, about 8 mole % dipalmitoylphosphatidylethanolamine-**polyethylene**

glycol 5,000 and about 10 mole % dipalmitoylphosphatidic acid. The carrier comprises a surfactant, preferably a fluorosurfactant. The compositions further comprise a telomerase. The compositions further comprise a fusion peptide. Preferred delivery compound - The compound to be delivered is a pharmaceutical agent, synthetic organic molecule, protein, peptide or genetic material, preferably a mutant gene that encodes a defective receptor chosen from tumor necrosis factor (TNF), gamma **interferon** (**IFN** gamma) or interleukin-1 (IL-1), antisense oligonucleotide (that preferably hybridizes to a nucleic acid molecule encoding a protein selected from TNF receptor, **IFN** gamma receptor or IL-1 receptor) or a ribozyme (a ribozyme that disrupts nucleic acid molecules encoding a protein chosen from TNF receptor, **IFN** gamma receptor or IL-1 receptor).
Preferred targeting ligand - The targeting ligand is a protein, antibody (fragment), hormone (analog), glycoprotein, lectin, (poly)peptide, amino acid, sugar, saccharide, carbohydrate, vitamin, steroid (analog), cofactor, bioactive agent or genetic material, preferably Sialyl Lewis X (preferred), mucin, hyaluronic acid, LFA-1, VLA-4, fibrinogen, von Willebrand factor, vitronectin, VCAM-1, CD49d/CD29, methyl-alpha-D-mannopyranoside, N-formal peptide, C5a, leukotriene B4, platelet-activating factor, IL-8/NAP-1, CTAP-III, beta-thromboglobulin, NAP-2, gro/MGSA, ENA-78, MCP-1, MAP-1alpha,beta, RANTES or I-309.
Preferred nuclear localization sequence - The nuclear localization sequence is a peptide, protein, receptor, transcription factor or an enzyme, especially influenza virus nucleoprotein, karyophenin beta1, human stat1 gene, m-importin, mouse homolog of nuclear pore targeting complex, hepatitis B virus (HBV) polymerase, glucocorticoids receptor (GlucR), **interferon**-regulated factors ISGF-3 and GAF, yeast mating switch/HO endonuclease promoter SW15, Drosophila melanogaster morphogen dorsal, nuclear factors NF-kappa and NF-AT, T-ag, c-rel, lamin B2, GrH receptor, c-fos, cofilin, rNFIL-6, NF-ATplc, PICA C-subunit, p42mapk/p44erk1, p90rsk, PKC-alpha, lodestar, v-jun, cyclin B (B-type cyclins), adenovirus 5 E1a protein, xnf7, PwA33, Rb-1, p53, c-myc, PTF1, HMG1/2 and tegument protein pp65 (UL83) of human cytomegalovirus. The nuclear localization sequence is a peptide comprising a defined amino acid sequence.

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